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(54) Title: BORONIC ACID AND ESTER INHIBITORS OF THROMBIN (57) Abstract Novel boronic acid derivatives of formula (I), which are useful inhibitors of trypsin-like enzymes, are disclosed: R ¹ -Z-CHR ² -BY ¹ Y ² .		

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Title

Boronic Acid and Ester Inhibitors of Thrombin

Field of the Invention

5 This invention relates to the discovery of new boronic acid derivatives which are inhibitors of thrombin and pharmaceutical compositions thereof.

Background of the Invention

10 Hemostasis is the normal physiological process in which bleeding from an injured blood vessel is arrested. It is a dynamic and complex process in which thrombin plays a key role. Blood coagulation may occur through either of two cascades of zymogen activations, the
15 extrinsic and intrinsic pathways of the coagulation cascade. The last protease in each pathway is thrombin, which acts to hydrolyze four small peptides (two FpA and two FpB) from each molecule of fibrinogen, thus deprotecting its polymerization sites. Once formed, the
20 linear fibrin polymers may be cross-linked by factor XIIIa, which is itself activated by thrombin. In addition, thrombin is a potent activator of platelets, upon which it acts at specific receptors. Thrombin activation of platelets leads to aggregation of the
25 cells and secretion of additional factors that further accelerate the creation of a hemostatic plug. Thrombin also potentiates its own production by the activation of factors V and VIII (see Hemker and Beguin in: Jolles, et. al., "Biology and Pathology of Platelet Vessel Wall
30 Interactions," pp. 219-26 (1986), Crawford and Scrutton in: Bloom and Thomas, "Haemostasis and Thrombosis," pp. 47-77, (1987), Bevers, et. al., *Eur. J. Biochem.* **1982**, 122, 429-36, Mann, *Trends Biochem. Sci.* **1987**, 12, 229-33).

35 Thrombosis may be regarded as the pathological condition wherein improper activity of the hemostatic

mechanism results in intravascular thrombus formation. Etiological factors such as the presence of atherosclerotic plaque, phlebitis and septicemia may cause thrombosis, leading to impaired blood flow to the effected tissues and possible serious pathological consequences.

Currently, two of the most effective classes of drugs in clinical use as anticoagulants are the heparins and the vitamin K antagonists. The heparins are ill-defined mixtures of sulfated polysaccharides that bind to, and thus potentiate the action of antithrombin III. Antithrombin III is a naturally occurring inhibitor of the activated clotting factors IXa, Xa, XIa, thrombin and probably XIIa (see Jaques, *Pharmacol. Rev.* 1980, 31, pp. 99-166). The vitamin K antagonists, of which warfarin is the most well-known example, act indirectly by inhibiting the post-ribosomal carboxylations of the vitamin K dependent coagulation factors II, VII, IX and X (see Hirsch, *Semin. Thromb. Hemostasis* 1986, 12, 1-11). While effective therapies for the treatment of thrombosis, heparins and vitamin K antagonists have the unfortunate side effects of bleeding and marked interpatient variability, resulting in a small and unpredictable therapeutic safety margin. The use of direct acting thrombin inhibitors is expected to alleviate these problems.

Thrombin is a serine protease having trypsin-like specificity for the cleavage of sequence-specific Arg-Xxx peptide bonds. As with other serine proteases, the cleavage event begins with an attack of the active site serine on the scissile bond of the substrate, resulting in the formation of a tetrahedral intermediate. This is followed by collapse of the tetrahedral intermediate to form an acyl enzyme and release of the amino terminus of the cleaved sequence. Hydrolysis of the acyl enzyme then releases the carboxy terminus.

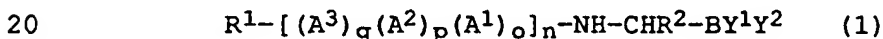
A number of naturally occurring thrombin inhibitors have been reported. These include nazumamide A from *Theonella* sp. (see Fusetani, et. al., *Tetrahedron Lett.* **1991**, 32, 7073-4), cyclotheonamide A from *Theonella* sp. (see Fusetani, et. al., *J. Am. Chem. Soc.* **1990**, 112, 7053-4), amblyommin from *Amblyomma hebraeum* (see Bonin, et. al., EP 345614), hirudin from *Hirudo medicinalis*, recombinant versions of hirudin and hirudin fragments (see Rigbl and Jackson, EP 352903, Koerwer, WO 9109946, Meyer, et. al., WO 9108233, Dawson, et. al., WO 9109125, Maraganore, et. al., WO 9102750 and Maraganore, EP 333356).

Synthetic thrombin inhibitors have also been disclosed. Arylsulfonylarginine amides such as (2R,4R)-4-methyl-1-[N²-(3-methyl-1,2,3,4-tetrahydro-8-quinolinyl)sulfonyl]-L-arginyl]-2-piperidinecarboxylate have been shown to be effective inhibitors of thrombin (see Okamoto, et. al. *Thromb Res.* **1976**, 8, 77-82, Ohshiro, et. al., *Blood Vessel* **1983**, 14, 216-8), as have compounds containing constrained arginine mimics such as (2-naphthylsulfonylglycyl)-4-amidino-phenylalanyl piperidide (see Stuerzebecher, et. al., *Thromb. Res.* **1983**, 29, 635-42), 1-[2-[5-(dimethylamino)naphth-1-ylsulfonylamido]-3-(2-iminohexahydropyrimidin-5-yl)propanoyl]-4-methylpiperidine dihydrochloride (see Ishikawa, JP 88227572 and Ishikawa and Inamura, JP 88227573), N-(trans-4-amino-methylcyclohexylcarbonyl)-4-O-(2-picolyl)-L-tyrosine 4-acetanilide dihydrochloride (see Okamoto, et. al., EP 217286) and 4-[(aminoiminomethyl)amino]benzoic acid esters (see Fuji, et. al., DE 3005580, Matsuoka, et. al., *Jpn. J. Pharmacol.* **1989**, 51, 455-63, and Takeshita, et. al., EP 435235).

Inhibitor design has benefitted from the knowledge of the mechanism of action and of the peptide sequences

which are thought to bind in the catalytic site of thrombin, e.g., -Gly-Val-Arg-Gly- of fibrinogen (see Blombäck, et. al., *J. Biol. Chem.*, **1972**, 247, 1496-512), Ile-Pro-Arg-Ser- of prothrombin (see Magnussen, et. al., in: Reich, et. al., "Proteases and Biological Control," pp. 123-149 (1975)) and -Val-Pro-Arg-Gly- of factor XIII (see Takagi and Doolittle, *Biochemistry* **1974**, 13, 750-6 and Nakamura, et. al., *Biochem. Biophys. Res. Commun.* **1974**, 58, 250-256). This class of mechanism-based inhibitors are exemplified by the tripeptide aldehyde D-Phe-Pro-N-Me-Arg-H (see Bajusz, et. al., *J. Med. Chem.* **1990**, 33, 1729-35), the chloromethyl ketone Ac-(D)-Phe-Pro-ArgCH₂Cl (see Kettner and Shaw, *Thromb. Res.* **1979**, 14, 969-73) and the trifluoromethyl ketone D-Phe-Pro-ArgCF₃ (see Kolb, et. al., US 697987).

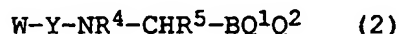
Kettner and Shenvi (EP 293881, published June 12, 1988), disclose peptide boronic acid inhibitors of trypsin-like proteases of formula (1)



wherein Y¹ and Y², independently, are hydroxyl or fluoro or, taken together, form a moiety derived from a dihydroxy compound having at least two hydroxy groups separated by at least two connecting atoms in a chain or ring, said chain or ring comprising 1 to about 20 carbon atoms and, optionally, a heteroatom which can be N, S, or O; R² is a substituted alkyl selected from the group consisting of -(CH₂)_z-X, -CH(CH₃)-(CH₂)₂-X, -CH₂-CH(CH₃)-CH₂-X, -(CH₂)₂-CH(CH₃)-X and -(CH₂)₂-CH(CH₃)-X, where X is -NH₂, -NH-C(NH)-NH₂ or -S-C(NH)-NH₂, and z is 3 to 5; n, o, p and q are, independently, either 0 or 1; A¹, A² and A³ are, independently, amino acids of L- or D-configuration selected from the group consisting of Ala, Arg, Asn, Asp, Cys, Gln, Glu, Gly, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr and Val; and R¹

is a peptide comprised of 1 to about 20 amino acids, an acyl or a sulfonyl group comprised of 1 to about 20 carbon atoms, H, or an N-terminal protecting group. In this disclosure, Kettner and Shenvi demonstrated that the pinanediol esters of boropeptides are pharmacologically equivalent to the corresponding boronic acids.

Metternich (EP 0471651 A2) discloses borolysine thrombin inhibitors of formula (2)

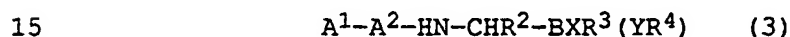


wherein W is an N-protecting group; Y is a sequence of n amino acids such that the n+1 amino acid peptide Y-Lys or Y-Arg has an affinity for the active site of a trypsin-like protease; where n is an integer of from 1 to 10 and in which at least one amino acid is an unnatural amino acid having a hydrophobic side chain; Q¹ and Q² are the same or different and are selected from -OH, -COR₁, -CONR₁R₂, -NR₁R₂ or -OR₃ of Q¹ and Q² taken together form a diol residue; R₁, R₂ and R₃ which may be the same or different, are C₁₋₁₀alkyl, C₆₋₁₀aryl, C₆₋₁₀aralkyl, or phenyl substituted by up to three groups selected from C₁₋₄alkyl, halogen and C₁₋₄alkoxy; R₄ is hydrogen or C₁₋₁₀alkyl; R₅ is a group -A-X; wherein A is -(CH₂)_z- in which z is 2, 3, 4 or 5; -CH(CH₃)-(CH₂)₂-; -CH₂-CH(CH₃)-CH₂-; -(CH₂)₂-CH(CH₃)-; -(CH₂)₂-C(CH₃)₂-; CH(CH₃)-(CH₂)₃-; -CH₂-CH(CH₃)-(CH₂)₂-; -CH₂-CH₂-CH(CH₃)-CH₂-; -(CH₂)₃-CH(CH₃)-; -(CH₂)₃-C(CH₃)₂; C₆₋₁₀aryl C₆₋₁₀aralkyl and X is -NH₂, -NH-C(NH)-NH₂, -S-C(NH)-NH₂, -N₃, -C₁₋₄alkoxy, C₁₋₄alkylthio or Si(CH₃)₃ or R₄ and R₅ taken together form a trimethylene group and the asymmetric carbon atom may have the D- or L-configuration or represent any mixture of these.

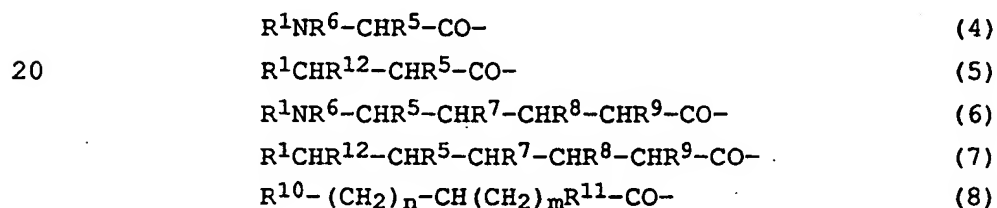
Surprising for their lack of a basic residue at P₁ are tripeptide thrombin inhibitors comprised of 1-

aminoboronic and 1-aminophosphonic acid analogs of 3-methoxy-propylglycine (see Claeson, et. al., US 07-245428) and pentylglycine (see Cheng, et. al., "Symposium on Thrombosis and Hemostasis," 1991, Amsterdam, Abstract 2150).

In addition to thrombin inhibition, boro-peptides have been disclosed with utility as a treatment for tumors, viral infections and arthritis (US 4963655A and EP 354522A), emphysema (US 4499082A), hypertension (EP 315574A) and as factor VII/VIIa inhibitors (WO 8909612A). Kleemann, et. al. (AU A-24693/88) disclose renin-inhibiting 1-amino boronic acid derivatives of formula (3)



in which A^1 denotes a radical of formulae (4-8).



Despite the foregoing, more efficacious and specific thrombin inhibitors are needed as potentially valuable therapeutic agents for the treatment of thrombosis. None of the cited references describe or suggest the new thrombin-inhibiting boronic acid derivatives of the present invention.

Summary of Invention

The present invention pertains to novel compounds of formula (I):



wherein

Y^1 and Y^2 are independently

- a) -OH,
- 10 b) -F,
- c) -NR³R⁴, or
- d) C1-C8-alkoxy;

Y^1 and Y^2 when taken together can form

- a) a cyclic boron ester where said chain or ring
- 15 contains from 2 to 20 carbon atoms and, optionally, a heteroatom which can be N, S, or O,
- b) a divalent cyclic boro amide where said chain or ring contains from 2 to 20 carbon atoms,
- c) a cyclic boro amide-ester where said chain or
- 20 ring contains from 2 to 20 carbon atoms;

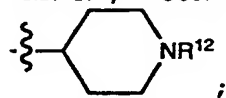
Z is

- a) -(CH₂)_mCONR⁸-,
- b) -(CH₂)_mCSNR⁸-,
- c) -(CH₂)_mSO₂NR⁸-,
- 25 d) -(CH₂)_mCO₂-,
- e) -(CH₂)_mC(S)O-, or
- f) -(CH₂)_mSO₂O-;

R¹ is

- a) -(CH₂)_p-aryl, wherein aryl is phenyl, naphthyl or
- 30 biphenyl substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, methylenedioxy, -R⁸, -OR⁸, -NO₂, -CF₃, -S(O)_rR⁷,

$-\text{NR}^8\text{R}^9$, $-\text{COR}^8$, $-\text{CO}_2\text{R}^8$, $-\text{CONR}^8\text{R}^9$, NR^8COR^9 ;



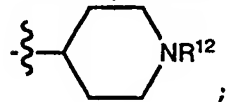
b) heteroaryl, wherein heteroaryl is an unsubstituted, monosubstituted or disubstituted:

- 5 i) 5- or 6-membered aromatic ring, which contains from 1 to 3 heteroatoms selected from the group consisting of O, N, and S,
- ii) quinolinyl,
- iii) isoquinolinyl,
- 10 iv) benzopyranyl,
- v) benzothiophenyl,
- vi) benzofuranyl,
- vii) 5,6,7,8-tetrahydroquinolinyl
- viii) 5,6,7,8-tetrahydroisoquinolinyl

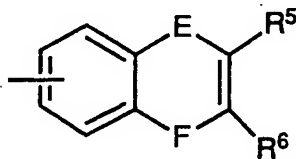
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and wherein the substituents are members selected from the group consisting of halo (F, Cl, Br, I), $-\text{CN}$, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-\text{R}^8$, $-\text{OR}^8$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{S}(\text{O})\text{R}^7$, $-\text{NR}^8\text{R}^9$, $-\text{COR}^8$, $-\text{CO}_2\text{R}^8$, $-\text{CONR}^8\text{R}^9$, NR^8COR^9 , NRCO_2R^9 ,

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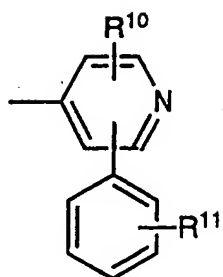


c)



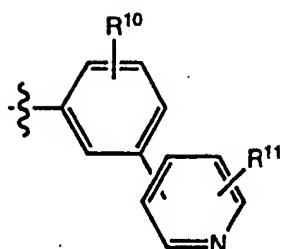
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d)



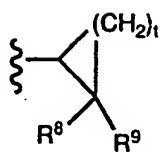
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e)



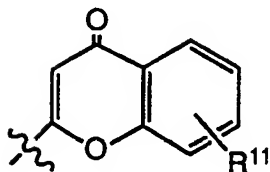
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f)



15

g)



R² is

a) $-(CH_2)_n-NHC(NH)NH_2$,

20 b) $-(CH_2)_n-NHC(NH)NHCOCH_3$,

- c) $-(CH_2)_n-SC(NH)NH_2$,
- d) $-(CH_2)_n-SC(NH)NHCOCH_3$,
- e) $-(CH_2)_n-NH_2$, or
- f) $-(CH_2)_n-NH(2\text{-pyridyl})$;

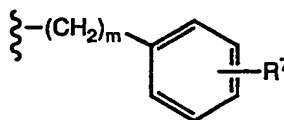
- 5 R^3 is H, phenyl or C1-C4-alkyl;
 R^4 is H or phenylsulfonyl;
 R^5 and R^6 are hydrogen or when taken together from a six membered aromatic ring optionally substituted with one, two or three substituents selected from the group
 10 consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, $-OR^8$, $-NO_2$, $-CF_3$, $-S(O)_2R^7$, $-NR^8R^9$, $-COR^8$, $-CO_2R^8$, $-CONR^8R^9$, phenyl, benzyl, phenylethyl;

R^7 is

- 15 a) phenyl,
 b) C1-C4-alkyl,
 c) C1-C4-alkoxy, or
 d) $-CF_3$;

R^8 and R^9 are independently

- 20 a) H,
 b)



- 25 c) C3-C7-cycloalkyl,
 d) C1-C8-alkyl;
 R^{10} and R^{11} are independently
 a) halo (F, Cl, Br, I),
 b) -CN,
 30 c) C1-C10-alkyl,
 d) C3-C8-cycloalkyl,
 e) C2-C10-alkenyl,
 f) C2-C10-alkynyl,
 g) $-OR^8$,

- h) $-\text{NO}_2$,
 i) $-\text{CF}_3$,
 j) $-\text{S}(\text{O})_r\text{R}^7$,
 5 k) $-\text{NR}^8\text{R}^9$,
 l) $-\text{COR}^9$,
 m) $-\text{CO}_2\text{R}^8$
 n) $-\text{CONR}^8\text{R}^9$;

R^{12} is

- 10 a) H,
 b) C1-C4-alkyl,
 c) phenyl,
 d) benzyl
 e) $-\text{COR}^7$
 15 f) $-\text{SO}_2\text{R}^7$

m is 0 to 6;

n is 3 or 4;

p is 0 to 2;

r is 0 to 2;

- 20 t is 1 to 5

E is $-\text{CO}-$, $-\text{SO}_2-$, $-\text{CH}_2-$ or a single bond,

F is $-\text{CO}-$; and pharmaceutically acceptable salts thereof.

- Preferred compounds of formula (I) are those
 25 compounds wherein R^1 is phenyl and biphenyl containing
 1-3 substituents selected from the series halo (F, Cl,
 Br, I), C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl,
 C2-C10-alkynyl, $-\text{R}^8$, $-\text{OR}^8$, $-\text{NO}_2$, $-\text{CF}_3$, $-\text{S}(\text{O})_r\text{R}^7$, $-\text{NR}^8\text{R}^9$,
 $-\text{COR}^8$, $-\text{CO}_2\text{R}^8$, $-\text{CONR}^8\text{R}^9$; NR^8COR^9 ;

- 30 R^2 is

- a) $-(\text{CH}_2)_3-\text{NHC}(\text{NH})\text{NH}_2$, or
 b) $-(\text{CH}_2)_3-\text{SC}(\text{NH})\text{NH}_2$.

More preferred are those preferred compounds wherein

Z is $-(\text{CH}_2)_m\text{CONR}^8-$.

35

Most preferred are those more preferred compounds listed below:

- N*¹-(4-phenylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(3-phenoxybenzoyl)-(R)-boroarginine, hydrochloride
5 *N*¹-(1-fluorenonyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-[1-butyl]benzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(2-benzoylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(5-phenyl-2-furoyl)-(R)-boroarginine, hydrochloride
*N*¹-(3-[N-benzyloxycarbonyl-N-methylamino]-4-[1-butyl]-
10 benzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(2-phenyl-4-isoquinolyl)-(R)-boroarginine,
hydrochloride
*N*¹-(4-cyclohexylbenzoyl)-(R)-boroarginine,
hydrochloride
15 *N*¹-(2-methyl-4-phenylbenzoyl)-(R)-boroarginine,
hydrochloride

Illustrative of the compounds of this invention are the following:

- 20 *N*¹-(4-phenylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
*N*¹-(3-phenylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
25 *N*¹-(3-phenoxybenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
*N*¹-(4-[4-pyridyl]benzoyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
*N*¹-(2-benzoylbenzoyl)-(R)-boroarginine (+)-pinanediol,
30 bisulfite
*N*¹-(3-benzoylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
*N*¹-(4-benzoylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite

35

- N^1 -(3-[*N*-benzyloxycarbonyl]aminobenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- N^1 -(3-[*N*-benzyloxycarbonyl-*N*-methyl]aminobenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- 5 N^1 -(4-ethylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
- N^1 -(4-*n*-propylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
- N^1 -(4-isopropylbenzoyl)-(R)-boroarginine (+)-pinanediol,
10 bisulfite
- N^1 -(4-*n*-butylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
- N^1 -(4-*tert*-butylbenzoyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
- 15 N^1 -(4-*n*-hexylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
- N^1 -(4-cyclohexylbenzoyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
- N^1 -(2-[*N*-(2-phenylethyl)carbonyl]aminobenzoyl)-(R)-
20 boroarginine (+)-pinanediol, bisulfite
- N^1 -(4-*n*-butyloxybenzoyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
- N^1 -(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- 25 N^1 -(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- N^1 -(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- N^1 -(4-[4-methoxy]phenylbenzoyl)-(R)-boroarginine (+)-
30 pinanediol, bisulfite
- N^1 -(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- N^1 -(2-[1-naphthyl]benzoyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
- 35 N^1 -(4-[4-carboxy]phenylbenzoyl)-(R)-boroarginine (+)-
pinanediol, bisulfite

- N^1 -(4-phenylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(3-phenylbenzoyl)-(R)-borothioarginine (+)-
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- 5 N^1 -(3-phenoxybenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(2-benzoylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(3-benzoylbenzoyl)-(R)-borothioarginine (+)-
10 pinanediol, hydrobromide
- N^1 -(4-benzoylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(3-[N-benzyloxycarbonyl]aminobenzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide
- 15 N^1 -(3-[N-benzyloxycarbonyl-N-methyl]aminobenzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide
- N^1 -(4-ethylbenzoyl)-(R)-borothioarginine (+)-pinanediol,
hydrobromide
- N^1 -(4-n-propylbenzoyl)-(R)-borothioarginine (+)-
20 pinanediol, hydrobromide
- N^1 -(4-isopropylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(4-n-butylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- 25 N^1 -(4-tert-butylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(4-n-hexylbenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N^1 -(4-cyclohexylbenzoyl)-(R)-borothioarginine (+)-
30 pinanediol, hydrobromide
- N^1 -(2-[N-(2-phenylethyl)carbonyl]aminobenzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide
- N^1 -(4-n-butyloxybenzoyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- 35 N^1 -(4-[N-cyclopropylcarbonyl]aminobenzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide

- N^1 -(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide
 N^1 -(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide
5 N^1 -(4-[4-methoxy]phenylbenzoyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
 N^1 -(2-[2-phenylbenzyloxycarbonyl]benzoyl)-(R)-
borothioarginine (+)-pinanediol, hydrobromide
 N^1 -(2-[1-naphthyl]benzoyl)-(R)-borothioarginine (+)-
10 pinanediol, hydrobromide
 N^1 -(4-[4-carboxy]phenylbenzoyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
 N^1 -([2-anthraquinonyl]carbonyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
15 N^1 -([2-dioxothioxanthinonyl]carbonyl)-(R)-boroarginine
(+)-pinanediol, bisulfite
 N^1 -([2-anthraquinonyl]carbonyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
 N^1 -([2-dioxothioxanthinonyl]carbonyl)-(R)-
20 borothioarginine (+)-pinanediol, hydrobromide
 N^1 -([2-fluoren-9-onyl]carbonyl)-(R)-borothiohomarginine
(+)-pinanediol, hydrobromide
 N^1 -([2-fluoren-9-onyl]carbonyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
25 N^1 -([2-fluoren-9-onyl]carbonyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
 N^1 -([3-fluoren-9-onyl]carbonyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
 N^1 -([3-fluoren-9-onyl]carbonyl)-(R)-boroarginine (+)-
30 pinanediol, bisulfite
 N^1 -([4-fluoren-9-onyl]carbonyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
 N^1 -([4-fluoren-9-onyl]carbonyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
35 N^1 -(1-naphthoyl)-(R)-borothioarginine (+)-pinanediol,
hydrobromide

- N*¹-(1-naphthoyl)-(R)-boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-phenyl-5-methoxybenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- 5 *N*¹-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-phenyl-5-fluorobenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(R)-
- 10 boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-phenyl-5-chlorobenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- 15 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(R)-
- 20 boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(R)-
- 25 boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(R)-boroethioarginine (+)-pinanediol, hydrobromide
- N*¹-(2-methyl-4-phenyl-5-methoxybenzoyl)-(R)-boroarginine (+)-pinanediol, bisulfite
- 30 *N*¹-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(R)-boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-phenyl-5-fluorobenzoyl)-(R)-boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(R)-
- 35 boroarginine (+)-pinanediol, bisulfite

- N*¹-(2-methyl-4-phenyl-5-chlorobenzoyl)-(R)-boroarginine
(+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(R)-boroarginine
(+)-pinanediol, bisulfite
- 5 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-
(R)-boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(R)-
10 boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-
trifluoromethylbenzoyl)-(R)-boroarginine (+)-pinanediol,
bisulfite
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(R)-
15 boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(R)-
boroarginine (+)-pinanediol, bisulfite
- N*¹-(2-[5-phenyl]furylcarbonyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
- 20 *N*¹-(2-[5-phenyl]thiophenylcarbonyl)-(R)-boroarginine
(+)-pinanediol, bisulfite
- N*¹-(2-[5-phenyl]furylcarbonyl)-(R)-borothioarginine (+)-
pinanediol, hydrobromide
- N*¹-(2-[5-phenyl]thiophen-ylcarbonyl)-(R)-
25 borothioarginine (+)-pinanediol, hydrobromide
- N*¹-(3-[6-phenyl]pyridylcarbonyl)-(R)-boroarginine (+)-
pinanediol, bisulfite
- N*¹-(3-[5-benzyloxy]pyridylcarbonyl)-(R)-boroarginine
(+)-pinanediol, bisulfite
- 30 *N*¹-(3-[6-phenyl]pyridylcarbonyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
- N*¹-(3-[5-benzyloxy]pyridylcarbonyl)-(R)-borothioarginine
(+)-pinanediol, hydrobromide
- N*¹-(2-benzopyronylcarbonyl)-(R)-boroarginine (+)-
35 pinanediol, bisulfite

- N*¹-(2-benzopyronylcarbonyl)-(R)-borothioarginine (+)-pinanediol, hydrobromide
*N*¹-(3-isoquinolinylcarbonyl)-(R)-boroarginine (+)-pinanediol, bisulfite
- 5 *N*¹-(2-phenyl-4-isoquinolinylcarbonyl)-(R)-boroarginine (+)-pinanediol, bisulfite
*N*¹-(3-isoquinolinylcarbonyl)-(R)-borothioarginine (+)-pinanediol, hydrobromide
*N*¹-(2-phenyl-4-isoquinolinylcarbonyl)-(R)-
- 10 borothioarginine (+)-pinanediol, hydrobromide
*N*¹-(2-isoquinolinylcarbonyl)-(R)-boroarginine (+)-pinanediol, bisulfite
*N*¹-(2-isoquinolinylcarbonyl)-(R)-borothioarginine (+)-pinanediol, hydrobromide
- 15 *N*¹-(4-phenylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(3-phenylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(3-phenoxybenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-[4-pyridyl]benzoyl)-(R)-boroarginine, hydrochloride
- 20 *N*¹-(2-benzoylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(3-benzoylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-benzoylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(3-[N-benzyloxycarbonyl]aminobenzoyl)-(R)-boroarginine, hydrochloride
- 25 *N*¹-(3-[N-benzyloxycarbonyl-N-methyl]aminobenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-ethylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-n-propylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-isopropylbenzoyl)-(R)-boroarginine, hydrochloride
- 30 *N*¹-(4-tert-butylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-n-hexylbenzoyl)-(R)-boroarginine, hydrochloride
*N*¹-(4-cyclohexylbenzoyl)-(R)-boroarginine, hydrochloride
- 35 *N*¹-(2-[N-(2-phenylethyl)carbonyl]aminobenzoyl)-(R)-boroarginine, hydrochloride

- N*¹-(4-*n*-butyloxybenzoyl)-(R)-boroarginine,
hydrochloride
- N*¹-(4-[*N*-cyclopropylcarbonyl]aminobenzoyl)-(R)-
boroarginine, hydrochloride
- 5 *N*¹-(4-[*N*-cyclohexylcarbonyl]aminobenzoyl)-(R)-
boroarginine, hydrochloride
- N*¹-(4-[*N*-(4-methoxy)benzoyl]aminobenzoyl)-(R)-
boroarginine, hydrochloride
- N*¹-(4-[4-methoxy]phenylbenzoyl)-(R)-boroarginine,
10 hydrochloride
- N*¹-(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(R)-
boroarginine, hydrochloride
- N*¹-(2-[1-naphthyl]benzoyl)-(R)-boroarginine,
hydrochloride
- 15 *N*¹-(4-[4-carboxy]phenylbenzoyl)-(R)-boroarginine,
hydrochloride
- N*¹-([2-anthraquinonyl]carbonyl)-(R)-boroarginine,
hydrochloride
- N*¹-([2-dioxothioxanthinonyl]carbonyl)-(R)-boroarginine,
20 hydrochloride
- N*¹-([2-fluoren-9-onyl]carbonyl)-(R)-boroarginine,
hydrochloride
- N*¹-([3-fluoren-9-onyl]carbonyl)-(R)-boroarginine,
hydrochloride
- 25 *N*¹-(1-naphthoyl)-(R)-boroarginine, hydrochloride
- N*¹-([4-fluoren-9-onyl]carbonyl)-(R)-boroarginine,
hydrochloride
- N*¹-(2-methyl-4-phenyl-5-methoxybenzoyl)-(R)-
boroarginine, hydrochloride
- 30 *N*¹-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(R)-
boroarginine, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-fluorobenzoyl)-(R)-boroarginine,
hydrochloride
- N*¹-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(R)-
35 boroarginine, hydrochloride

- N*¹-(2-methyl-4-phenyl-5-chlorobenzoyl)-(R)-boroarginine,
hydrochloride
- N*¹-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(R)-
boroarginine, hydrochloride
- 5 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(R)-
boroarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-
(R)-boroarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(R)-
10 boroarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-
trifluoromethylbenzoyl)-(R)-boroarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(R)-
boroarginine, hydrochloride
- 15 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(R)-
boroarginine, hydrochloride
- N*¹-(2-[5-phenyl]furylcarbonyl)-(R)-boroarginine,
hydrochloride
- N*¹-(2-[5-phenyl]thiophenylcarbonyl)-(R)-boroarginine,
20 hydrochloride
- N*¹-(2-benzopyranylcabonyl)-(R)-boroarginine,
hydrochloride
- N*¹-(2-isoquinolinylcarbonyl)-(R)-boroarginine,
hydrochloride
- 25 *N*¹-(3-isoquinolinylcarbonyl)-(R)-boroarginine,
hydrochloride
- N*¹-(2-phenyl-4-isoquinolinylcarbonyl)-(R)-boroarginine,
hydrochloride
- N*¹-(4-phenylbenzoyl)-(R)-borothioarginine,
30 hydrochloride
- N*¹-(3-phenylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N*¹-(3-phenoxybenzoyl)-(R)-borothioarginine,
hydrochloride
- 35 *N*¹-(2-benzoylbenzoyl)-(R)-borothioarginine,
hydrochloride

- N^1 -(3-benzoylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N^1 -(4-benzoylbenzoyl)-(R)-borothioarginine,
hydrochloride
- 5 N^1 -(3-[N-benzyloxycarbonyl]aminobenzoyl)-(R)-
borothioarginine, hydrochloride
- N^1 -(3-[N-benzyloxycarbonyl-N-methyl]aminobenzoyl)-(R)-
borothioarginine, hydrochloride
- N^1 -(4-ethylbenzoyl)-(R)-borothioarginine, hydrochloride
- 10 N^1 -(4-n-propylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N^1 -(4-isopropylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N^1 -(4-n-butylbenzoyl)-(R)-borothioarginine,
15 hydrochloride
- N^1 -(4-tert-butylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N^1 -(4-n-hexylbenzoyl)-(R)-borothioarginine,
hydrochloride
- 20 N^1 -(4-cyclohexylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N^1 -(2-[N-(2-phenylethyl) carbonyl]aminobenzoyl)-(R)-
borothioarginine, hydrochloride
- N^1 -(4-n-butyloxybenzoyl)-(R)-borothioarginine,
25 hydrochloride
- N^1 -(4-[N-cyclopropylcarbonyl]aminobenzoyl)-(R)-
borothioarginine, hydrochloride
- N^1 -(4-[N-cyclohexylcarbonyl]aminobenzoyl)-(R)-
borothioarginine, hydrochloride
- 30 N^1 -(4-[N-(4-methoxy)benzoyl]aminobenzoyl)-(R)-
borothioarginine, hydrochloride
- N^1 -(4-[4-methoxy]phenylbenzoyl)-(R)-borothioarginine,
hydrochloride
- N^1 -(2-[2-phenylbenzyloxycarbonyl]benzoyl)-(R)-
35 borothioarginine, hydrochloride

- N*¹-(2-[1-naphthyl]benzoyl)-(R)-boroethioarginine,
hydrochloride
- N*¹-(4-[4-carboxy]phenylbenzoyl)-(R)-boroethioarginine,
hydrochloride
- 5 *N*¹-([2-anthraquinonyl]carbonyl)-(R)-boroethioarginine,
hydrochloride
- N*¹-([2-dioxothioxanthinonyl]carbonyl)-(R)-
boroethioarginine, hydrochloride
- N*¹-([2-fluoren-9-onyl]carbonyl)-(R)-
10 boroethiohomoarginine, hydrochloride
- N*¹-([2-fluoren-9-onyl]carbonyl)-(R)-boroethioarginine,
hydrochloride
- N*¹-([3-fluoren-9-onyl]carbonyl)-(R)-boroethioarginine,
hydrochloride
- 15 *N*¹-([4-fluoren-9-onyl]carbonyl)-(R)-boroethioarginine,
hydrochloride
- N*¹-(1-naphthoyl)-(R)-boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-methoxybenzoyl)-(R)-
boroethioarginine, hydrochloride
- 20 *N*¹-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(R)-
boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-fluorobenzoyl)-(R)-
boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(R)-
25 boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-chlorobenzoyl)-(R)-
boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(R)-
boroethioarginine, hydrochloride
- 30 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(R)-
boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-
(R)-boroethioarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(R)-
35 boroethioarginine, hydrochloride

- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(R)-borothioarginine, hydrochloride
- 5 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(R)-borothioarginine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(R)-borothioarginine, hydrochloride
- N*¹-(2-[5-phenyl]furylcarbonyl)-(R)-borothioarginine, hydrochloride
- 10 *N*¹-(2-[5-phenyl]thiophenylcarbonyl)-(R)-borothioarginine, hydrochloride
- N*¹-(3-[6-phenyl]pyridylcarbonyl)-(R)-boroarginine, hydrochloride
- N*¹-(3-[5-benzyloxy]pyridylcarbonyl)-(R)-boroarginine, hydrochloride
- 15 *N*¹-(3-[6-phenyl]pyridylcarbonyl)-(R)-borothioarginine, hydrochloride
- N*¹-(3-[5-benzyloxy]pyridylcarbonyl)-(R)-borothioarginine, hydrochloride
- 20 *N*¹-(2-benzopyronylcarbonyl)-(R)-borothioarginine, hydrochloride
- N*¹-(3-isoquinolinylcarbonyl)-(R)-borothioarginine, hydrochloride
- N*¹-(2-phenyl-4-isoquinolinylcarbonyl)-(R)-borothioarginine, hydrochloride
- 25 *N*¹-(2-isoquinolinylcarbonyl)-(R)-borothioarginine, hydrochloride
- N*¹-(4-phenylbenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 30 *N*¹-(3-phenylbenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(3-phenoxybenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(4-[4-pyridyl]benzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 35

- N^1 -(2-benzoylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(3-benzoylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- 5 N^1 -(4-benzoylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(3-[N-benzyloxycarbonyl]aminobenzoyl)-(R)-borolysine
(+)-pinanediol, hydrochloride
- N^1 -(3-[N-benzyloxycarbonyl-N-methyl]aminobenzoyl)-(R)-
10 borolysine (+)-pinanediol, hydrochloride
- N^1 -(4-ethylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(4-n-propylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- 15 N^1 -(4-isopropylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(4-tert-butylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(4-n-hexylbenzoyl)-(R)-borolysine (+)-pinanediol,
20 hydrochloride
- N^1 -(4-cyclohexylbenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(2-[N-(2-phenylethyl)carbonyl]aminobenzoyl)-(R)-
borolysine (+)-pinanediol, hydrochloride
- 25 N^1 -(4-n-butyloxybenzoyl)-(R)-borolysine (+)-pinanediol,
hydrochloride
- N^1 -(4-[N-cyclopropylcarbonyl]aminobenzoyl)-(R)-
borolysine (+)-pinanediol, hydrochloride
- N^1 -(4-[N-cyclohexylcarbonyl]aminobenzoyl)-(R)-borolysine
30 (+)-pinanediol, hydrochloride
- N^1 -(4-[N-(4-methoxy)benzoyl]aminobenzoyl)-(R)-borolysine
(+)-pinanediol, hydrochloride
- N^1 -(4-[4-methoxy]phenylbenzoyl)-(R)-borolysine (+)-
pinanediol, hydrochloride
- 35 N^1 -(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(R)-borolysine
(+)-pinanediol, hydrochloride

- N*¹-(2-[1-naphthyl]benzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(4-[4-carboxy]phenylbenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 5 *N*¹-([2-anthraquinonyl]carbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-([2-dioxothioxanthinonyl]carbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-([2-fluoren-9-onyl]carbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 10 *N*¹-([3-fluoren-9-onyl]carbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(1-naphthoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 15 *N*¹-([4-fluoren-9-onyl]carbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-methoxybenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 20 *N*¹-(2-methyl-4-phenyl-5-fluorobenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 25 *N*¹-(2-methyl-4-phenyl-5-chlorobenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 30 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride

- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-trifluoromethylbenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 5 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-[5-phenyl]furylcarbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 10 *N*¹-(2-[5-phenyl]thiophen-ylcarbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-benzopyranylcabonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-isoquinolinylcarbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 15 *N*¹-(3-isoquinolinylcarbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- N*¹-(2-phenyl-4-isoquinolinylcarbonyl)-(R)-borolysine (+)-pinanediol, hydrochloride
- 20 *N*¹-(4-phenylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(3-phenylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(3-phenoxybenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(4-[4-pyridyl]benzoyl)-(R)-borolysine, hydrochloride
- N*¹-(2-benzoylbenzoyl)-(R)-borolysine, hydrochloride
- 25 *N*¹-(3-benzoylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(4-benzoylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(3-[N-benzyloxycarbonyl]aminobenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(3-[N-benzyloxycarbonyl-N-methyl]aminobenzoyl)-(R)-borolysine, hydrochloride
- 30 *N*¹-(4-ethylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(4-n-propylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(4-isopropylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(4-tert-butylbenzoyl)-(R)-borolysine, hydrochloride
- 35 *N*¹-(4-n-hexylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(4-cyclohexylbenzoyl)-(R)-borolysine, hydrochloride

- N^1 -(2-[N-(2-phenylethyl)carbonyl]aminobenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(4-n-butylloxybenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(4-[N-cyclopropylcarbonyl]aminobenzoyl)-(R)-borolysine, hydrochloride
- 5 N^1 -(4-[N-cyclohexylcarbonyl]aminobenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(4-[N-(4-methoxy)benzoyl]aminobenzoyl)-(R)-borolysine, hydrochloride
- 10 N^1 -(4-[4-methoxy]phenylbenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(2-[2-phenyl]benzyloxycarbonylbenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(2-[1-naphthyl]benzoyl)-(R)-borolysine, hydrochloride
- 15 N^1 -(4-[4-carboxy]phenylbenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(2-anthraquinonyl)carbonyl)-(R)-borolysine, hydrochloride
- 20 N^1 -(2-dioxothioxanthinonyl)carbonyl)-(R)-borolysine, hydrochloride
- N^1 -(2-fluoren-9-onyl)carbonyl)-(R)-borolysine, hydrochloride
- N^1 -(3-fluoren-9-onyl)carbonyl)-(R)-borolysine, hydrochloride
- 25 N^1 -(1-naphthoyl)-(R)-borolysine, hydrochloride
- N^1 -(4-fluoren-9-onyl)carbonyl)-(R)-borolysine, hydrochloride
- N^1 -(2-methyl-4-phenyl-5-methoxybenzoyl)-(R)-borolysine, hydrochloride
- 30 N^1 -(2-methyl-4-phenyl-5-carboxamidobenzoyl)-(R)-borolysine, hydrochloride
- N^1 -(2-methyl-4-phenyl-5-fluorobenzoyl)-(R)-borolysine, hydrochloride
- 35 N^1 -(2-methyl-4-phenyl-5-trifluoromethylbenzoyl)-(R)-borolysine, hydrochloride

- N*¹-(2-methyl-4-phenyl-5-chlorobenzoyl)-(R)-borolysine,
hydrochloride
- N*¹-(2-methyl-4-phenyl-5-hydroxybenzoyl)-(R)-borolysine,
hydrochloride
- 5 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-methoxybenzoyl)-(R)-
borolysine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-carboxamidobenzoyl)-
(R)-borolysine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-fluorobenzoyl)-(R)-
10 borolysine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-
trifluoromethylbenzoyl)-(R)-borolysine, hydrochloride
- N*¹-(2-methyl-4-[4-carboxy]phenyl-5-chlorobenzoyl)-(R)-
borolysine, hydrochloride
- 15 *N*¹-(2-methyl-4-[4-carboxy]phenyl-5-hydroxybenzoyl)-(R)-
borolysine, hydrochloride
- N*¹-(2-[5-phenyl]furylcarbonyl)-(R)-borolysine,
hydrochloride
- N*¹-(2-[5-phenyl]thiophen-ylcarbonyl)-(R)-borolysine,
20 hydrochloride
- N*¹-(2-benzopyranylcabonyl)-(R)-borolysine,
hydrochloride
- N*¹-(2-isoquinolinylcarbonyl)-(R)-borolysine,
hydrochloride
- 25 *N*¹-(3-isoquinolinylcarbonyl)-(R)-borolysine,
hydrochloride
- N*¹-(2-phenyl-4-isoquinolinylcarbonyl)-(R)-borolysine,
hydrochloride
- N*¹-(2-methyl-4-phenylbenzoyl)-R-borolysine,
30 hydrochloride
- N*¹-(2-methyl-4-phenylbenzoyl)-R-borolysine, (+)-
pinanediol, hydrochloride
- N*¹-(2-methyl-4-phenylbenzoyl)-R-borothioarginine (+)-
hydrobromide
- 35 *N*¹-(2-methyl-4-phenylbenzoyl)-R-borothioarginine (+)-
pinanediol, hydrochloride

*N*¹-(2-methyl-4-phenylbenzoyl)-R-boroarginine (+)-hydrochloride

*N*¹-(2-methyl-4-phenylbenzoyl)-R-boroarginine (+)-pinanediol, bisulfite

5

Detailed Description of the Invention

Throughout the specification, the following conventional three-letter abbreviations for amino acid residues or amino acids apply:

	Ala =	alanine
	Arg =	arginine
	Asn =	asparagine
	Asp =	aspartic acid
15	Cys =	cysteine
	Gln =	glutamine
	Glu =	glutamic acid
	Gly =	glycine
	His =	histidine
20	Ile =	isoleucine
	Leu =	leucine
	Lys =	lysine
	Met =	methionine
	Phe =	phenylalanine
25	Pro =	proline
	Ser =	serine
	Thr =	threonine
	Trp =	tryptophan
	Tyr =	tyrosine
30	Val =	valine

The prefix "boro" indicates amino acid residues where the carboxy group is replaced by a boronic acid (Formula I, Y¹ and Y² = -OH).

The pinanediol boronic acid ester and the pinacol boronic acid ester are abbreviated "-C₁₀H₁₆" and

35

"-C₆H₁₂" respectively. Other illustrations of diols useful for deriving boronic acid esters are 1,2-ethanediol, 1,3-propanediol, 1,2-propanediol, 2,3-butanediol, 1,2-diisopropylethanediol, 5,6-decanediol, 5 1,2-dicyclohexylethanediol.

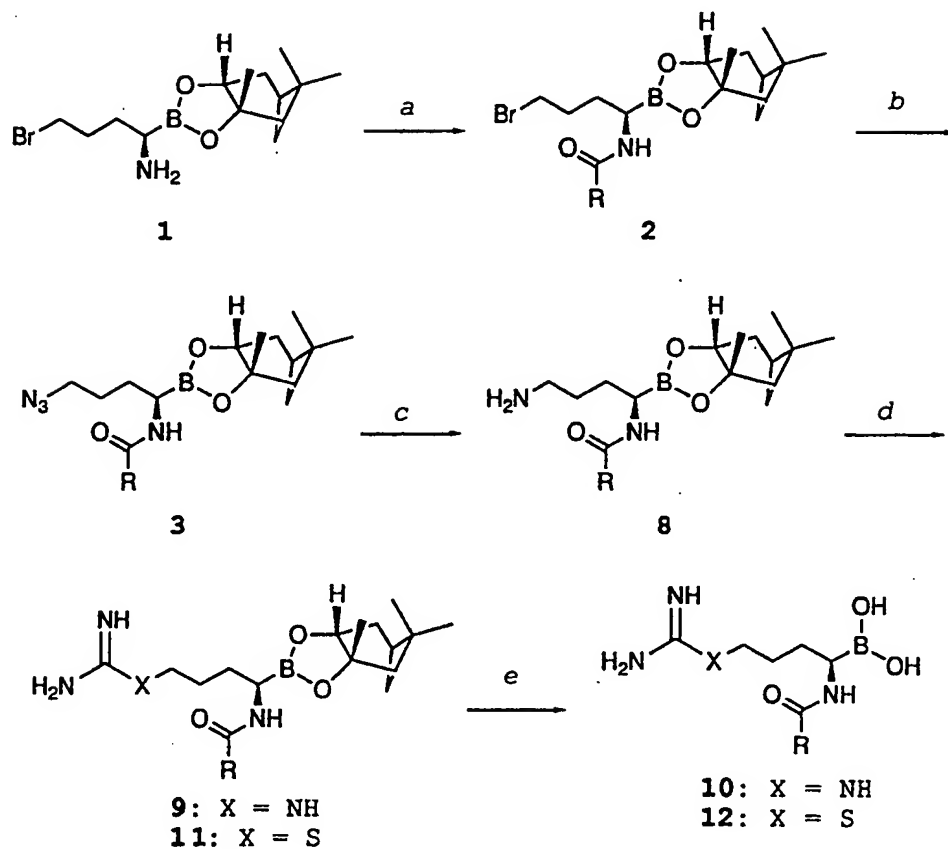
Note that throughout the text when an alkyl substituent is mentioned, the normal alkyl structure is meant (e.g. butyl is n-butyl) unless otherwise specified. However, in the definition of radicals above 10 (e.g. R³), both branched and straight chains are included in the scope of alkyl.

It is understood that many of the compounds of the present invention contain one or more chiral centers and that these stereoisomers may possess distinct physical and biological properties. The present invention 15 comprises all of the stereoisomers or mixtures thereof. If the pure enantiomers or diastereomers are desired, they may be prepared using starting materials with the appropriate stereochemistry, or may be separated from 20 mixtures of undesired stereoisomers by standard techniques, including chiral chromatography and recrystallization of diastereomeric salts.

Synthesis

The compounds of formula (I) can be prepared using 25 the reactions and techniques described below. The reactions are performed in a solvent appropriate to the reagents and materials employed and suitable for the transformations being affected. It will be understood by those skilled in the art of organic synthesis that 30 the functionality present on the molecule should be consistent with the chemical transformations proposed and this will sometimes require judgment as to the order of synthetic steps or selection of particular process scheme used from that shown below in order to obtain a 35 desired compound of the invention.

5

Scheme 1. Synthesis of Thrombin Inhibitors

Reagents: a. IBCF, NMM, RCO_2H , Et_3N , 0°C , b. NaN_3 , c. H_2 , $\text{Pd}(\text{OH})_2/\text{C}$, HCl , d. DMAP, aminoiminomethanesulfonic acid, e. phenylboronic acid

10

Amine hydrochloride 1 is readily available via the procedure of Kettner and Shenvi (EP 0293881 A2).

There are numerous synthetic methods by which to prepare amide 2, however, competing with amide formation is the cyclization of 1 to afford a complex mixture containing the desired amide and the corresponding *N*-acylboroproline. Since purification at this stage is unfeasible, choosing the correct method for amide formation is crucial to obtaining 2 in a purity suitable for subsequent synthetic transformations.

Three methods are preferred for the preparation of 2.

10 In the first, a solution of 1 in tetrahydrofuran or dichloromethane at 0 °C is treated sequentially with the desired acid chloride followed by two equivalents of triethylamine. The mixture is then allowed to warm to room temperature overnight. The second method is the

15 mixed anhydride procedure of Anderson, et. al. (*J. Am. Chem. Soc.* 1967, 89, 5012). In this method the isobutyl mixed anhydride is generated by dissolving the carboxylic acid component in tetrahydrofuran and adding one equivalent of *N*-methyldmorpholine. The solution is

20 cooled to 0 °C and one equivalent of isobutyl chloroformate is added. After 5 minutes, a solution of 1 in chloroform is added, followed by the addition of one equivalent of triethylamine. The mixture is typically stirred at 0 °C for one hour followed by one

25 to several hours at room temperature. The third method for amide formation is the hydroxybenzotriazole/DCC method of König and Geiger (*Chem. Ber.* 1970, 103, 788-98). Thus, to a solution of 1 and the carboxylic acid component in dimethylformamide or tetrahydrofuran at 0

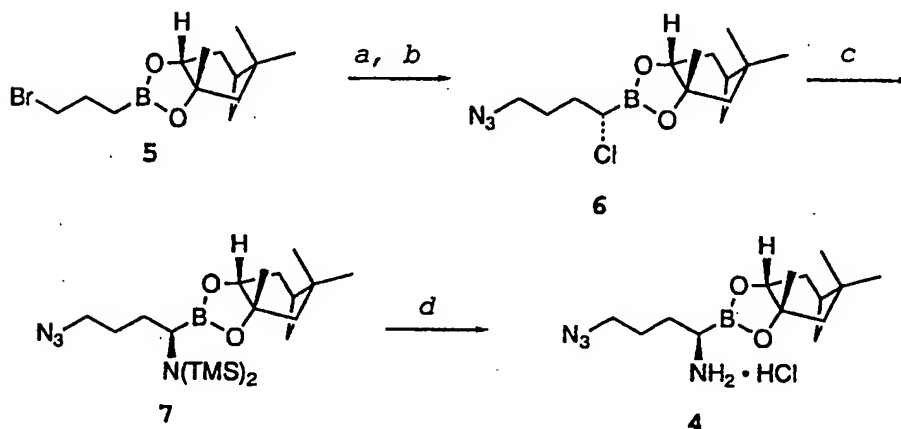
30 °C is added *N*-methyldmorpholine, 1-hydroxybenzotriazole hydrate (2 eq) and DCC (1.05 eq). The solution is allowed to warm to room temperature overnight.

The preferred method for the preparation of azide 3 is by reaction of 2 with sodium azide (1.1 eq) in

35 dimethylformamide at 70 °C for 2 hours.

The azide displacement may also be performed prior to amide formation. This is the preferred method in cases where the rate of amide formation is slow relative to the rate of cyclization. Azide 4 is prepared by a
 5 modification of the procedure of Kettner and Shenvi (EP 0293881 A2) as shown in Scheme 2. Thus, bromide 5 is reacted with sodium azide, followed by homologation to give 6, chloride displacement to afford 7 and acidic
 10 hydrolysis to give 4. Amide formation between 4 and the carboxylic acid component then affords 3 directly.

Scheme 2. Synthesis of Azide 4



Reagents: a. NaN_3 b. CHCl_2Li , ZnCl_2 , c. $\text{LiN}(\text{TMS})_2$,
 d. 4M HCl , dioxane

15

Reduction of azide 3 to amine 8 may be accomplished by hydrogenation over precious metal catalysts. The preferred catalyst for this transformation is Pearlman's catalyst (palladium hydroxide on carbon). The amine is
 20 typically isolated as the hydrochloride salt. Isolation of 8 as the free base typically results in lowered yields. Salts of 8 which may confer superior physical properties may be preferred over the hydrochloride salt.

Formamidination of amine 8 may be accomplished using
 25 cyanamide. Due to the low reactivity of amine 8,

however, the preferred method for this transformation is reaction with 4-dimethylaminopyridine (DMAP) and aminoiminomethanesulfonic acid (AMSA, prepared by the method of Kim, et. al., *Tetrahedron Lett.* 1988, 29, 3183-6). This affords guanidine 9, which is isolated as the bisulfite or hydrochloride salt.

Cleavage of pinanediol ester 9 may be accomplished using anhydrous boron trichloride according to the procedure of Matteson and Ray (*J. Am. Chem. Soc.* 1980, 102, 7588). This method, however, is strongly Lewis acidic and leads to partial destruction of the substrate. The preferred method for water soluble boronic acids is a transesterification reaction that is run in the presence of excess phenylboronic acid. The free boronic acid 10 may then be isolated using cation exchange chromatography.

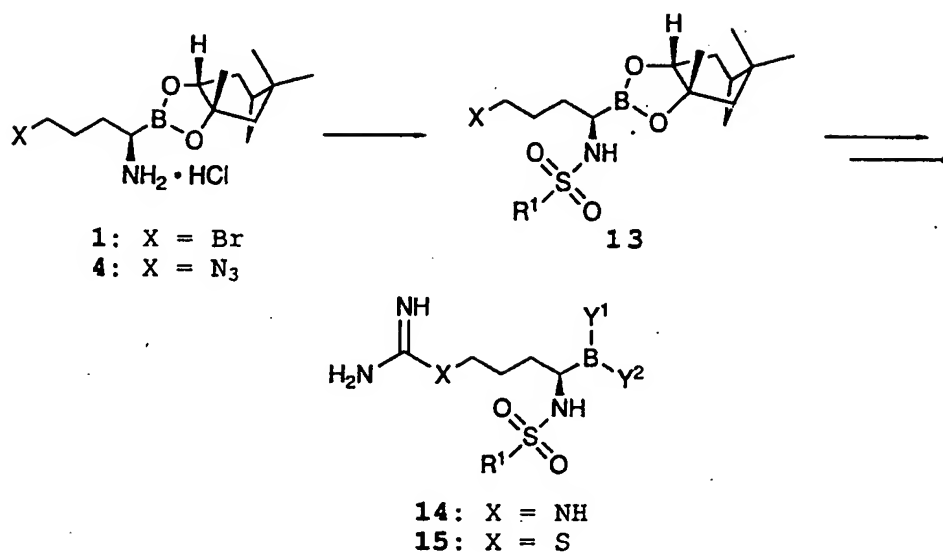
The isothiuronium functionalized analogs 11/12 are prepared from bromide 2 according to the procedure of Kettner and Shenvi (EP 0293881 A2).

Inhibitors containing a sulfonamide in place of a carboxamide are prepared from either 1 or 4 by reaction with a sulfonyl chloride in the presence of a hindered amine (Scheme 3). The product sulfonamide 13 is then converted to the guanidinium 14 or isothiuronium 15 in the same manner as the corresponding carboxamides.

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Scheme 3. Synthesis of Sulfonamides

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Inhibitors containing the borolysine moiety are prepared analogously to those containing boroarginine according to Kettner and Shenvi (EP 0293881 A2).

Novel biaryls synthesized in this invention are prepared through palladium catalyzed coupling of an appropriate arylmetal species to the aryl halide of choice using the methods described in Negishi, et. al., *Org. Synth.* **1987**, 66, 67-74, and references cited within.

20

EXAMPLE 1: *N*¹-(4-Phenylbenzoyl)boroarginine (+)-Pinanediol, Bisulfite

Part A: (+)-Pinanediol 4-bromo-1(R)-(4-phenylbenzo-
yl)aminobutane-1-boronate. To a solution of (+)-
pinanediol 4-bromo-1(R)-aminobutane-1-boronate
hydrochloride (5.00 g, 13.6 mmol) in dichloromethane (50
5 mL) at 0 °C was added 4-phenylbenzoyl chloride (4.97 g,
22.9 mmol) followed by *N*-methylmorpholine (4 mL, 36
mmol). After 1 hour, the cooling bath was removed and
the mixture stirred at room temperature for 2 hours.
The mixture was then diluted with ethyl acetate and
10 washed with 0.1 M hydrochloric acid, saturated sodium
bicarbonate and saturated sodium chloride. The organic
phase was dried over anhydrous magnesium sulfate,
filtered and the filtrate concentrated *in vacuo* to
afford 3.37 g (48%) of the desired amide, mass spectrum:
15 (M+H)⁺ = 510/512; ¹H NMR (300 MHz, CDCl₃) δ7.9 (2H, d, J
= 8.3), 7.84 (1H, bs), 7.6 (2H, d, J = 8.3), 7.44 (5H,
m), 4.37 (1H, m), 3.41 (1H, t, J = 6.9), 2.0 (10H, m)
1.49 (3H, s), 1.38 (1H, m), 1.29 (3H, s), 0.91 (3H, s).

20 Part B: (+)-Pinanediol 4-azido-1(R)-(4-phenylbenzo-
yl)aminobutane-1-boronate. To a solution of (+)-
pinanediol 4-bromo-1(R)-(4-phenylbenzoyl)aminobutane-1-
boronate (3.37 g, 6.60 mmol) in dimethylformamide (6 mL)
was added sodium azide (547 mg, 8.41 mmol). The
25 resulting mixture was heated at 70 °C for 2 hours,
cooled to room temperature, and diluted with ethyl
acetate. The mixture was then washed with water,
saturated sodium chloride and dried over anhydrous
magnesium sulfate. Filtration, followed by
30 concentration of the filtrate *in vacuo* gave 3.04 g (97%)
of the desired azide, mass spectrum: (M+H)⁺ = 473; ¹H
NMR (300 MHz, CDCl₃) δ7.89 (2H, d, J = 8.3), 7.75 (1H,
bs), 7.3 (7H, m), 4.32 (1H, m), 3.32 (1H, m), 2.0 (10H,
m) 1.48 (3H, s), 1.3 (4H, m), 0.9 (3H, s).

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Part C: N^1 -(4-Phenylbenzoyl)boroornithine (+)-pinanediol, hydrochloride. To a solution of (+)-pinanediol 4-azido-1(R)-(4-phenylbenzoyl)aminobutane-1-boronate (3.04 g, 6.44 mmol) in methanol (30 mL) was
5 added Pearlman's catalyst $\text{Pd}(\text{OH})_2/\text{C}$, 200 mg) and 1 M hydrochloric acid (6.5 mL, 6.5 mmol). The mixture was placed on a Parr apparatus and hydrogenated at 50 psi for 3 hours. The mixture was filtered using Celite™, washed with methanol and the filtrate concentrated in
10 vacuo. The resulting amorphous solid was dissolved in water and washed with ether. The aqueous phase was then concentrated in vacuo and crystallized from ethyl acetate-hexanes, giving 1.52 g (49%) of the desired amine hydrochloride, mass spectrum: $(\text{M}+\text{H})^+ = 447$; mp:
15 157-170 °C; ^1H NMR (400 MHz, $\text{CDCl}_3/\text{DMSO}-d_6$) δ 9.88 (1H, bs), 8.18, (2H, d, $J = 8.3$), 8.13 (3H, bs), 7.68 (2H, d, $J = 8.3$), 7.61 (2H, d, $J = 7.0$), 7.45 (2H, d, $J = 7.0$), 7.37 (1H, d, $J = 7.30$), 4.20 (1H, d, $J = 6.3$), 2.99 (1H, m), 2.87 (2H, m), 2.31 (1H, m), 2.13 (1H, m), 1.84 (7H, m),
20 1.56 (1H, d, $J = 10.0$), 1.42 (3H, s), 1.29 (3H, s), 0.89 (3H, s).

Part D: N^1 -(4-Phenylbenzoyl)boroarginine (+)-pinanediol, bisulfite. To a solution of N^1 -(4-phenylbenzoyl)boroornithine (+)-pinanediol,
25 hydrochloride (80 mg, 0.17 mmol) in ethanol (2 mL) was added 4-dimethylaminopyridine (40 mg, 0.33 mmol). After 15 minutes, aminoiminomethanesulfonic acid (40 mg, 0.32 mmol) was added and the resulting mixture heated at
30 reflux for 3 hours. After cooling to room temperature, the mixture was filtered and the filtrate concentrated in vacuo. The residue was dissolved in chloroform and washed with 0.1 M hydrochloric acid, water and dried over anhydrous magnesium sulfate. Filtration, followed
35 by concentration of the filtrate in vacuo afforded 73 mg

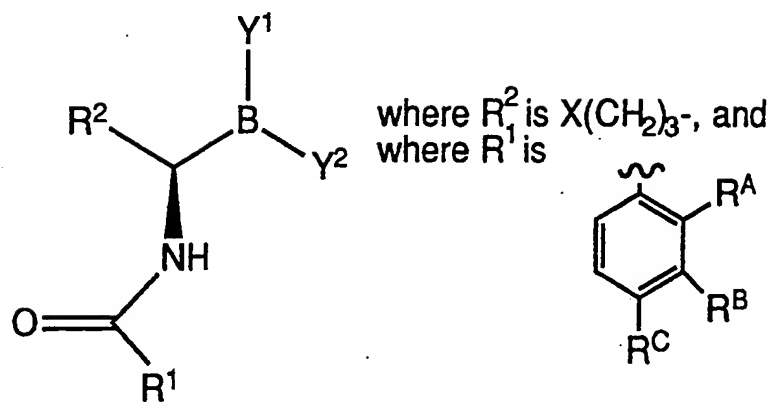
(84%) of the desired guanidine, mass spectrum: $(M+H)^+ = 489$; 1H NMR (400 MHz, $CDCl_3$, 60 °C) δ 9.48 (1H, bs), 8.10 (2H, d, $J = 8.1$), 8.07 (1H, bs), 7.75 (1H, bs), 7.54 (2H, d, $J = 8.3$), 7.48 (2H, d, $J = 7.0$), 7.35 (3H, m), 5 7.06 (4H, bs), 4.19 (1H, bd, $J = 8.3$), 3.1 (2H, m), 2.84 (1H, m), 2.29 (1H, m), 2.12 (1H, m), 1.96 (1H, m), 1.75 (6H, m), 1.47 (1H, d, $J = 10.2$), 1.40 (3H, s), 1.24 (3H, s), 0.83 (3H, s).

10 EXAMPLE 34: (+)-Pinanediol 4-(Formamidino)thio-1(R)-(4-phenylbenzoyl)aminobutane-1-boronate, Hydrobromide

(+)-Pinanediol 4-(formamidino)thio-1(R)-(4-phenylbenzoyl)aminobutane-1-boronate, hydrobromide. To
15 a solution of (+)-pinanediol 4-bromo-1(R)-(4-phenylbenzoyl)aminobutane-1-boronate (200 mg, 0.392 mmol) in methanol (3 mL) was added thiourea (120 mg, 1.58 mmol). The reaction was stirred at room temperature for 3 days. The mixture was concentrated *in vacuo*, the residue
20 dissolved in water and washed with ether. Concentration of the aqueous portion afforded 80 mg (35%) of the desired isothiurea, mass spectrum: $(M+H)^+ = 506$; 1H NMR (300 MHz, $CDCl_3$) δ 8.15 (2H, d, $J = 8.4$), 7.61 (2H, d, $J = 8.4$), 7.52 (2H, m), 7.38 (3H, m), 6.47 (1H, bs), 4.23
25 (1H, dd, $J = 6.6, 1.9$), 3.24 (1H, m), 3.14, (1H, m), 2.96, (1H, m), 2.32 (1H, m), 2.15 (1H, m), 1.99 (1H, m), 1.78 (6H, m), 1.48 (1H, d, $J = 10.1$), 1.42 (3H, s), 1.27 (3H, s), 0.86 (3H, s).

30 The compounds listed in Tables 1-12 can be prepared using the above examples.

TABLE 1



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Ex	X	R^A	R^B	R^C	Y^1, Y^2	Phys Data
10	1 NHC(NH)NH ₂	H	H	Ph	(+)-pinanediol	A
	2 NHC(NH)NH ₂	H	Ph	H	(+)-pinanediol	
	3 NHC(NH)NH ₂	H	OPh	Ph	(+)-pinanediol	B
	4 NHC(NH)NH ₂	H	H	4-pyridyl	(+)-pinanediol	C
	5 NHC(NH)NH ₂	COPh	H	H	(+)-pinanediol	
15	6 NHC(NH)NH ₂	H	COPh	H	(+)-pinanediol	
	7 NHC(NH)NH ₂	H	H	COPh	(+)-pinanediol	
	8 NHC(NH)NH ₂	H	NHCbz	H	(+)-pinanediol	
	9 NHC(NH)NH ₂	H	NMeCbz	H	(+)-pinanediol	
	10 NHC(NH)NH ₂	H	H	Et	(+)-pinanediol	
20	11 NHC(NH)NH ₂	H	H	n-Pr	(+)-pinanediol	
	12 NHC(NH)NH ₂	H	H	i-Pr	(+)-pinanediol	
	13 NHC(NH)NH ₂	H	H	n-Bu	(+)-pinanediol	
	14 NHC(NH)NH ₂	H	H	t-Bu	(+)-pinanediol	
	15 NHC(NH)NH ₂	H	H	n-hexyl	(+)-pinanediol	
25	16 NHC(NH)NH ₂	H	H	cyclohexyl	(+)-pinanediol	
	17 NHC(NH)NH ₂	NHCO(CH ₂) ₂ Ph	H	H	(+)-pinanediol	

	18	NHC (NH) NH ₂	H	H	O-n-Bu	(+)-pinanediol	
	19	NHC (NH) NH ₂	H	H	NHCOcyclopropyl	(+)-pinanediol	
	Ex	X	R ^A	R ^B	R ^C	Y ¹ , Y ²	Phys Data
5	20	NHC (NH) NH ₂	H	H	NHCO-cyclohexyl	(+)-pinanediol	
	21	NHC (NH) NH ₂	H	H	NHCO (4-C ₆ H ₄ OMe)	(+)-pinanediol	
	22	NHC (NH) NH ₂	H	H	4-C ₆ H ₄ OMe	(+)-pinanediol	
	23	NHC (NH) NH ₂	CO ₂ CH ₂ (2-C ₆ H ₄ Ph)	H	H	(+)-pinanediol	
10	24	NHC (NH) NH ₂	H	H	1-naphthyl	(+)-pinanediol	
	25	NHC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ H	(+)-pinanediol	
	26	NHC (NH) NH ₂	COPh	H	Me	(+)-pinanediol	
	27	NHC (NH) NH ₂	H	NHCbz	n-Bu	(+)-pinanediol	
	28	NHC (NH) NH ₂	H	NMeCbz	n-Bu	(+)-pinanediol	
15	29	NHC (NH) NH ₂	Me	H	Ph	(+)-pinanediol	QQ
	30	NHC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ H	(+)-pinanediol	
	31	NHC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ Me	(+)-pinanediol	
	32	NHC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ Me	(+)-pinanediol	
	33	NHC (NH) NH ₂	H	OMe	Ph	(+)-pinanediol	
20	34	SC (NH) NH ₂	H	H	Ph	(+)-pinanediol	D
	35	SC (NH) NH ₂	H	Ph	H	(+)-pinanediol	E
	36	SC (NH) NH ₂	H	OPh	H	(+)-pinanediol	F
	37	SC (NH) NH ₂	COPh	H	H	(+)-pinanediol	G
	38	SC (NH) NH ₂	H	COPh	H	(+)-pinanediol	H
25	39	SC (NH) NH ₂	H	H	COPh	(+)-pinanediol	I
	40	SC (NH) NH ₂	H	NHCbz	H	(+)-pinanediol	J
	41	SC (NH) NH ₂	H	NMeCbz	H	(+)-pinanediol	K
	42	SC (NH) NH ₂	H	H	Et	(+)-pinanediol	L
	43	SC (NH) NH ₂	H	H	n-Pr	(+)-pinanediol	M
30	44	SC (NH) NH ₂	H	H	i-Pr	(+)-pinanediol	N
	45	SC (NH) NH ₂	H	H	n-Bu	(+)-pinanediol	O
	46	SC (NH) NH ₂	H	H	t-Bu	(+)-pinanediol	P
	47	SC (NH) NH ₂	H	H	n-hexyl	(+)-pinanediol	Q
	48	SC (NH) NH ₂	H	H	cyclohexyl	(+)-pinanediol	R
35	49	SC (NH) NH ₂	NHCOCH ₂ CH ₂ Ph	H	H	(+)-pinanediol	S
	50	SC (NH) NH ₂	H	H	O-n-Bu	(+)-pinanediol	T

	51	SC (NH) NH ₂	H	H	NHCOcyclopropyl	(+)-pinanediol	U
	Ex	X	R ^A	R ^B	R ^C	Y ¹ , Y ²	Phys. Data
5	52	SC (NH) NH ₂	H	H	NHCOcyclohexyl	(+)-pinanediol	V
	53	SC (NH) NH ₂	H	H	NHCO(4-C ₆ H ₄ OMe)	(+)-pinanediol	W
	54	SC (NH) NH ₂	H	H	4-C ₆ H ₄ OMe	(+)-pinanediol	X
	55	SC (NH) NH ₂	CO ₂ CH ₂ (2-C ₆ H ₄ Ph)	H	H	(+)-pinanediol	Y
	56	SC (NH) NH ₂	H	H	1-naphthyl	(+)-pinanediol	
10	57	SC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ H	(+)-pinanediol	
	58	SC (NH) NH ₂	H	NHCBz	n-Bu	(+)-pinanediol	Z
	59	SC (NH) NH ₂	H	NMeCbz	n-Bu	(+)-pinanediol	AA
	60	SC (NH) NH ₂	COPh	H	Me	(+)-pinanediol	BB
	61	SC (NH) NH ₂	H	H	4-pyridyl	(+)-pinanediol	
15	62	SC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ H	(+)-pinanediol	
	63	SC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ Me	(+)-pinanediol	
	64	SC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ Me	(+)-pinanediol	
	65	SC (NH) NH ₂	Me	H	Ph	(+)-pinanediol	
	66	SC (NH) NH ₂	H	OMe	Ph	(+)-pinanediol	
20	67	CH ₂ NH ₂	H	H	Ph	(+)-pinanediol	
	68	CH ₂ NH ₂	H	Ph	H	(+)-pinanediol	
	69	CH ₂ NH ₂	H	OPh	H	(+)-pinanediol	
	70	CH ₂ NH ₂	COPh	H	H	(+)-pinanediol	
	71	CH ₂ NH ₂	H	COPh	H	(+)-pinanediol	
25	72	CH ₂ NH ₂	H	H	COPh	(+)-pinanediol	
	73	CH ₂ NH ₂	H	NHCBz	H	(+)-pinanediol	
	74	CH ₂ NH ₂	H	NMeCbz	H	(+)-pinanediol	
	75	CH ₂ NH ₂	H	H	Et	(+)-pinanediol	
	76	CH ₂ NH ₂	H	H	n-Pr	(+)-pinanediol	
30	77	CH ₂ NH ₂	H	H	i-Pr	(+)-pinanediol	
	78	CH ₂ NH ₂	H	H	n-Bu	(+)-pinanediol	
	79	CH ₂ NH ₂	H	H	t-Bu	(+)-pinanediol	
	80	CH ₂ NH ₂	H	H	n-hexyl	(+)-pinanediol	
	81	CH ₂ NH ₂	H	H	cyclohexyl	(+)-pinanediol	
35	82	CH ₂ NH ₂	NHCOCH ₂ CH ₂ Ph	H	H	(+)-pinanediol	
	83	CH ₂ NH ₂	H	H	O-n-Bu	(+)-pinanediol	

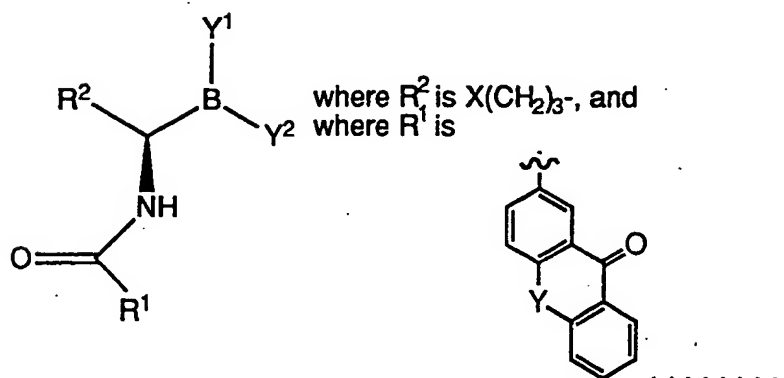
	84	CH ₂ NH ₂	H	H	NHCOcyclopropyl	(+)-pinanediol	
	Ex	X	R ^A	R ^B	R ^C	Y ¹ , Y ²	Phys:
							Date:
		85	CH ₂ NH ₂	H	H	NHCOcyclohexyl	(+)-pinanediol
5		86	CH ₂ NH ₂	H	H	NHCO(4-C ₆ H ₄ OMe)	(+)-pinanediol
		87	CH ₂ NH ₂	H	H	4-C ₆ H ₄ OMe	(+)-pinanediol
		88	CH ₂ NH ₂	CO ₂ CH ₂ (2-C ₆ H ₄ Ph)	H	H	(+)-pinanediol
		89	CH ₂ NH ₂	H	H	1-naphthyl	(+)-pinanediol
		90	CH ₂ NH ₂	H	H	4-C ₆ H ₄ CO ₂ H	(+)-pinanediol
10		91	CH ₂ NH ₂	H	NHCbz	n-Bu	(+)-pinanediol
		92	CH ₂ NH ₂	H	NMeCbz	n-Bu	(+)-pinanediol
		93	CH ₂ NH ₂	COPh	H	Me	(+)-pinanediol
		94	CH ₂ NH ₂	H	H	4-pyridyl	(+)-pinanediol
		95	CH ₂ NH ₂	Me	H	4-C ₆ H ₄ CO ₂ H	(+)-pinanediol
15		96	CH ₂ NH ₂	H	H	4-C ₆ H ₄ CO ₂ Me	(+)-pinanediol
		97	CH ₂ NH ₂	Me	H	4-C ₆ H ₄ CO ₂ Me	(+)-pinanediol
		98	CH ₂ NH ₂	Me	H	Ph	(+)-pinanediol
		99	CH ₂ NH ₂	H	OMe	Ph	(+)-pinanediol
		100	CH ₂ NH ₂	H	OMe	Ph	H, H
20		101	NHC(NH)NH ₂	H	H	Ph	H, H
		102	NHC(NH)NH ₂	H	Ph	H	H, H
		103	NHC(NH)NH ₂	H	OPh	Ph	H, H
		104	NHC(NH)NH ₂	H	H	4-pyridyl	H, H
		105	NHC(NH)NH ₂	COPh	H	H	H, H
25		106	NHC(NH)NH ₂	H	COPh	H	H, H
		107	NHC(NH)NH ₂	H	H	COPh	H, H
		108	NHC(NH)NH ₂	H	NHCbz	H	H, H
		109	NHC(NH)NH ₂	H	NMeCbz	H	H, H
		110	NHC(NH)NH ₂	H	H	Et	H, H
30		111	NHC(NH)NH ₂	H	H	n-Pr	H, H
		112	NHC(NH)NH ₂	H	H	i-Pr	H, H
		113	NHC(NH)NH ₂	H	H	n-Bu	H, H
		114	NHC(NH)NH ₂	H	H	t-Bu	H, H
		115	NHC(NH)NH ₂	H	H	n-hexyl	H, H
35		116	NHC(NH)NH ₂	H	H	cyclohexyl	H, H
		117	NHC(NH)NH ₂	NHCO(CH ₂) ₂ Ph	H	H	H, H

Ex	X	R ^A	R ^B	R ^C	y ¹ , y ²	Phys Data
5	118 NHC (NH) NH ₂	H	H	O-n-Bu	H, H	
	119 NHC (NH) NH ₂	H	H	NHCocyclopropyl	H, H	
	120 NHC (NH) NH ₂	H	H	NHCO-cyclohexyl	H, H	
	121 NHC (NH) NH ₂	H	H	NHCO (4-C ₆ H ₄ OMe)	H, H	
	122 NHC (NH) NH ₂	H	H	4-C ₆ H ₄ OMe	H, H	
10	123 NHC (NH) NH ₂	CO ₂ CH ₂ (2-C ₆ H ₄ Ph)	H	H	H, H	
	124 NHC (NH) NH ₂	H	H	1-naphthyl	H, H	
	125 NHC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ H	H, H	
	126 NHC (NH) NH ₂	COPh	H	Me	H, H	
	127 NHC (NH) NH ₂	H	NHCbz	n-Bu	H, H	
15	128 NHC (NH) NH ₂	H	NMeCbz	n-Bu	H, H	
	129 NHC (NH) NH ₂	Me	H	Ph	H, H	
	130 NHC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ H	H, H	
	131 NHC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ Me	H, H	
	132 NHC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ Me	H, H	
20	133 NHC (NH) NH ₂	H	OMe	Ph	H, H	
	134 SC (NH) NH ₂	H	H	Ph	H, H	
	135 SC (NH) NH ₂	H	Ph	H	H, H	
	136 SC (NH) NH ₂	H	OPh	H	H, H	
	137 SC (NH) NH ₂	COPh	H	H	H, H	
25	138 SC (NH) NH ₂	H	COPh	H	H, H	
	139 SC (NH) NH ₂	H	H	COPh	H, H	
	140 SC (NH) NH ₂	H	NHCbz	H	H, H	
	141 SC (NH) NH ₂	H	NMeCbz	H	H, H	
	142 SC (NH) NH ₂	H	H	Et	H, H	
30	143 SC (NH) NH ₂	H	H	n-Pr	H, H	
	144 SC (NH) NH ₂	H	H	i-Pr	H, H	
	145 SC (NH) NH ₂	H	H	n-Bu	H, H	
	146 SC (NH) NH ₂	H	H	t-Bu	H, H	
	147 SC (NH) NH ₂	H	H	n-hexyl	H, H	
35	148 SC (NH) NH ₂	H	H	cyclohexyl	H, H	
	149 SC (NH) NH ₂	NHCOCH ₂ CH ₂ Ph	H	H	H, H	
	150 SC (NH) NH ₂	H	H	O-n-Bu	H, H	
Ex	X	R ^A	R ^B	R ^C	y ¹ , y ²	Phys

						Date:
5	151	SC (NH) NH ₂	H	H	NHCO (CH ₂) ₂ phenyl	H, H RR
	152	SC (NH) NH ₂	H	H	NHCOcyclohexyl	H, H
	153	SC (NH) NH ₂	H	H	NHCO (4-C ₆ H ₄ OMe)	H, H
	154	SC (NH) NH ₂	H	H	4-C ₆ H ₄ OMe	H, H
	155	SC (NH) NH ₂	CO ₂ CH ₂ (2-C ₆ H ₄ Ph)	H	H	H, H
10	156	SC (NH) NH ₂	H	H	1-naphthyl	H, H
	157	SC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ H	H, H
	158	SC (NH) NH ₂	H	NHCbz	n-Bu	H, H
	159	SC (NH) NH ₂	H	NMeCbz	n-Bu	H, H
	160	SC (NH) NH ₂	COPh	H	Me	H, H
15	161	SC (NH) NH ₂	H	H	4-pyridyl	H, H
	162	SC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ H	H, H
	163	SC (NH) NH ₂	H	H	4-C ₆ H ₄ CO ₂ Me	H, H
	164	SC (NH) NH ₂	Me	H	4-C ₆ H ₄ CO ₂ Me	H, H
	165	SC (NH) NH ₂	Me	H	Ph	H, H
20	166	SC (NH) NH ₂	H	OMe	Ph	H, H
	167	CH ₂ NH ₂	H	H	Ph	H, H
	168	CH ₂ NH ₂	H	Ph	H	H, H
	169	CH ₂ NH ₂	H	OPh	H	H, H
	170	CH ₂ NH ₂	COPh	H	H	H, H
25	171	CH ₂ NH ₂	H	COPh	H	H, H
	172	CH ₂ NH ₂	H	H	COPh	H, H
	173	CH ₂ NH ₂	H	NHCbz	H	H, H
	174	CH ₂ NH ₂	H	NMeCbz	H	H, H
	175	CH ₂ NH ₂	H	H	Et	H, H
30	176	CH ₂ NH ₂	H	H	n-Pr	H, H
	177	CH ₂ NH ₂	H	H	i-Pr	H, H
	178	CH ₂ NH ₂	H	H	n-Bu	H, H
	179	CH ₂ NH ₂	H	H	t-Bu	H, H
	180	CH ₂ NH ₂	H	H	n-hexyl	H, H
35	181	CH ₂ NH ₂	H	H	cyclohexyl	H, H
	182	CH ₂ NH ₂	NHCOCH ₂ CH ₂ Ph	H	H	H, H
	183	CH ₂ NH ₂	H	H	O-n-Bu	H, H
	Ex	X	R ^A	R ^B	R ^C	y ¹ , y ² Phys
						Date:

	184	CH ₂ NH ₂	H	H NHCOCyclopropyl	H, H
	185	CH ₂ NH ₂	H	H NHCOCyclohexyl	H, H
	186	CH ₂ NH ₂	H	H NHCO (4-C ₆ H ₄ OMe)	H, H
	187	CH ₂ NH ₂	H	H 4-C ₆ H ₄ OMe	H, H
5	188	CH ₂ NH ₂ CO ₂ CH ₂ (2-C ₆ H ₄ Ph)	H	H	H, H
	189	CH ₂ NH ₂	H	H 1-naphthyl	H, H
	190	CH ₂ NH ₂	H	H 4-C ₆ H ₄ CO ₂ H	H, H
	191	CH ₂ NH ₂	H NHCbz	n-Bu	H, H
	192	CH ₂ NH ₂	H NMeCbz	n-Bu	H, H
10	193	CH ₂ NH ₂	COPh	H Me	H, H
	194	CH ₂ NH ₂	H	H 4-pyridyl	H, H
	195	CH ₂ NH ₂	Me	H 4-C ₆ H ₄ CO ₂ H	H, H
	196	CH ₂ NH ₂	H	H 4-C ₆ H ₄ CO ₂ Me	H, H
	197	CH ₂ NH ₂	Me	H 4-C ₆ H ₄ CO ₂ Me	H, H
15	198	CH ₂ NH ₂	Me	H Ph	H, H

TABLE 2

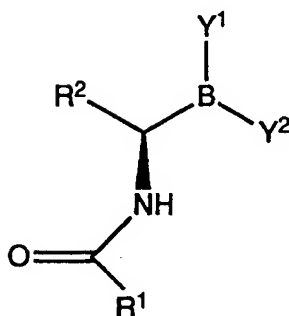


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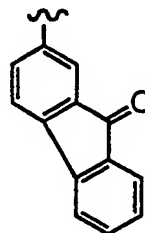
Ex	X	Y	y ¹ , y ²	Phys Data
199	CH ₂ NH ₂	CO	(+)-pinanediol	
25 200	CH ₂ NH ₂	SO ₂	(+)-pinanediol	
201	NHC(NH)NH ₂	CO	(+)-pinanediol	
Ex	X	Y	y ¹ , y ²	Phys

					Data
	202	NHC(NH)NH ₂	SO ₂	(+)-pinanediol	
	203	SC(NH)NH ₂	CO	(+)-pinanediol	CC
	204	SC(NH)NH ₂	SO ₂	(+)-pinanediol	DD
5	205	CH ₂ NH ₂	CO	H, H	
	206	CH ₂ NH ₂	SO ₂	H, H	
	207	NHC(NH)NH ₂	CO	H, H	
	208	NHC(NH)NH ₂	SO ₂	H, H	
	209	SC(NH)NH ₂	CO	H, H	
10	210	SC(NH)NH ₂	SO ₂	H, H	

TABLE 3



where R² is XCH₂(CH₂)CH₂-, and
where R¹ is



15

	Ex	X	t	y ¹ , y ²	Phys Data
	211	NH ₂	2	(+)-pinanediol	
	212	SC(NH)NH ₂	2	(+)-pinanediol	EE
20	213	SC(NH)NH ₂	1	(+)-pinanediol	FF
	214	NHC(NH)NH ₂	2	(+)-pinanediol	
	215	NHC(NH)NH ₂	1	(+)-pinanediol	
	216	NH ₂	2	H, H	
	217	SC(NH)NH ₂	2	H, H	

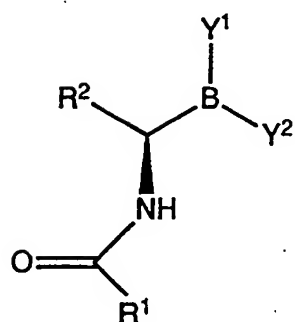
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Ex	X	T	y ¹ , y ²	Phys
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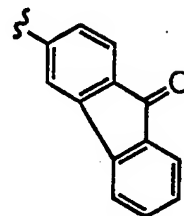
Data

	218	SC (NH) NH ₂	1	H, H
	219	NHC (NH) NH ₂	2	H, H
5	220	NHC (NH) NH ₂	1	H, H

TABLE 4

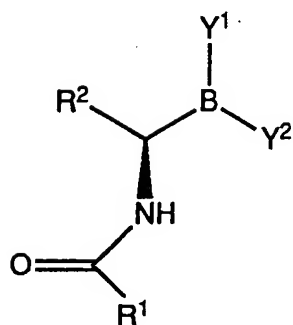


where R_2 is $X(CH_2)_3$, and
where R_1 is

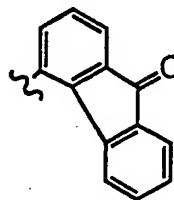


10	Ex	X	Y^1, Y^2	Phys Data
	221	CH ₂ NH ₂	(+)-pinanediol	
	222	NHC (NH) NH ₂	(+)-pinanediol	
	223	SC (NH) NH ₂	(+)-pinanediol	GG
	224	CH ₂ NH ₂	H, H	
15	225	NHC (NH) NH ₂	H, H	
	226	SC (NH) NH ₂	H, H	

TABLE 5

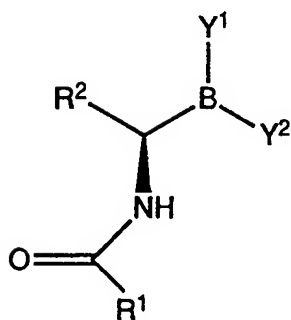


where R^2 is $X(CH_2)_3-$, and
where R^1 is

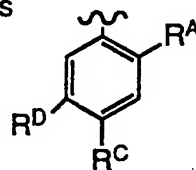


Ex	X	Y^1, Y^2	Phys Data
5 227	CH_2NH_2	(+)-pinanediol	
228	$NHC(NH)NH_2$	(+)-pinanediol	
229	$SC(NH)NH_2$	(+)-pinanediol	HH
230	CH_2NH_2	H, H	
231	$NHC(NH)NH_2$	H, H	
10 232	$SC(NH)NH_2$	H, H	

TABLE 6



where R^2 is $X(CH_2)_3-$, and
where R^1 is



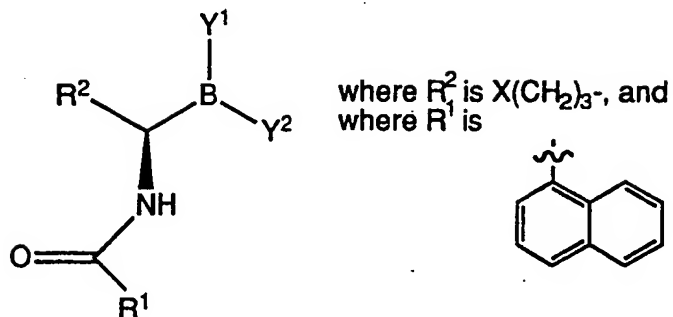
	Ex	X	R ^A	R ^C	R ^D	y ¹ , y ²	Phys Data
	233	NHC(NH)NH ₂	Me	Ph	OMe	(+)-pinanediol	
	234	NHC(NH)NH ₂	Me	Ph	CONH ₂	(+)-pinanediol	
	235	NHC(NH)NH ₂	Me	Ph	F	(+)-pinanediol	
5	236	NHC(NH)NH ₂	Me	Ph	CF ₃	(+)-pinanediol	
	237	NHC(NH)NH ₂	Me	Ph	Cl	(+)-pinanediol	
	238	NHC(NH)NH ₂	Me	Ph	OH	(+)-pinanediol	
	239	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OMe	(+)-pinanediol	
	240	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CONH ₂	(+)-pinanediol	
10	241	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	F	(+)-pinanediol	
	242	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CF ₃	(+)-pinanediol	
	243	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	Cl	(+)-pinanediol	
	244	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OH	(+)-pinanediol	
	245	SC(NH)NH ₂	Me	Ph	OMe	(+)-pinanediol	
15	246	SC(NH)NH ₂	Me	Ph	CONH ₂	(+)-pinanediol	
	247	SC(NH)NH ₂	Me	Ph	F	(+)-pinanediol	
	248	SC(NH)NH ₂	Me	Ph	CF ₃	(+)-pinanediol	
	249	SC(NH)NH ₂	Me	Ph	Cl	(+)-pinanediol	
	250	SC(NH)NH ₂	Me	Ph	OH	(+)-pinanediol	
20	251	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OMe	(+)-pinanediol	
	252	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CONH ₂	(+)-pinanediol	
	253	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	F	(+)-pinanediol	
	254	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CF ₃	(+)-pinanediol	
	255	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	Cl	(+)-pinanediol	
25	256	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OH	(+)-pinanediol	
	257	CH ₂ NH ₂	Me	Ph	OMe	(+)-pinanediol	
	258	CH ₂ NH ₂	Me	Ph	CONH ₂	(+)-pinanediol	
	259	CH ₂ NH ₂	Me	Ph	F	(+)-pinanediol	
	260	CH ₂ NH ₂	Me	Ph	CF ₃	(+)-pinanediol	
30	261	CH ₂ NH ₂	Me	Ph	Cl	(+)-pinanediol	
	262	CH ₂ NH ₂	Me	Ph	OH	(+)-pinanediol	
	263	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OMe	(+)-pinanediol	
	264	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CONH ₂	(+)-pinanediol	
	265	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	F	(+)-pinanediol	
35	266	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CF ₃	(+)-pinanediol	
	Ex	X	R ^A	R ^C	R ^D	y ¹ , y ²	Phys Data

	267	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	Cl	(+)-pinanediol	
	268	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OH	(+)-pinanediol	
	269	NHC(NH)NH ₂	Me	Ph	OMe	H, H	
	270	NHC(NH)NH ₂	Me	Ph	CONH ₂	H, H	
5	271	NHC(NH)NH ₂	Me	Ph	F	H, H	
	272	NHC(NH)NH ₂	Me	Ph	CF ₃	H, H	
	273	NHC(NH)NH ₂	Me	Ph	Cl	H, H	
	274	NHC(NH)NH ₂	Me	Ph	OH	H, H	
	275	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OMe	H, H	
10	276	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CONH ₂	H, H	
	277	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	F	H, H	
	278	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CF ₃	H, H	
	279	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	Cl	H, H	
	280	NHC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OH	H, H	
15	281	SC(NH)NH ₂	Me	Ph	OMe	H, H	
	282	SC(NH)NH ₂	Me	Ph	CONH ₂	H, H	
	283	SC(NH)NH ₂	Me	Ph	F	H, H	
	284	SC(NH)NH ₂	Me	Ph	CF ₃	H, H	
	285	SC(NH)NH ₂	Me	Ph	Cl	H, H	
20	286	SC(NH)NH ₂	Me	Ph	OH	H, H	
	287	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OMe	H, H	
	288	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CONH ₂	H, H	
	289	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	F	H, H	
	290	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CF ₃	H, H	
25	291	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	Cl	H, H	
	292	SC(NH)NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OH	H, H	
	293	CH ₂ NH ₂	Me	Ph	OMe	H, H	
	294	CH ₂ NH ₂	Me	Ph	CONH ₂	H, H	
	295	CH ₂ NH ₂	Me	Ph	F	H, H	
30	296	CH ₂ NH ₂	Me	Ph	CF ₃	H, H	
	297	CH ₂ NH ₂	Me	Ph	Cl	H, H	
	298	CH ₂ NH ₂	Me	Ph	OH	H, H	
	299	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OMe	H, H	
	300	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CONH ₂	H, H	
35	Ex	X	R ^A	R ^C	R ^D	Y ¹ , Y ²	Phys Data
	301	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	F	H, H	

302	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	CF ₃	H, H
303	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	Cl	H, H
304	CH ₂ NH ₂	Me	4-C ₆ H ₄ CO ₂ H	OH	H, H

5

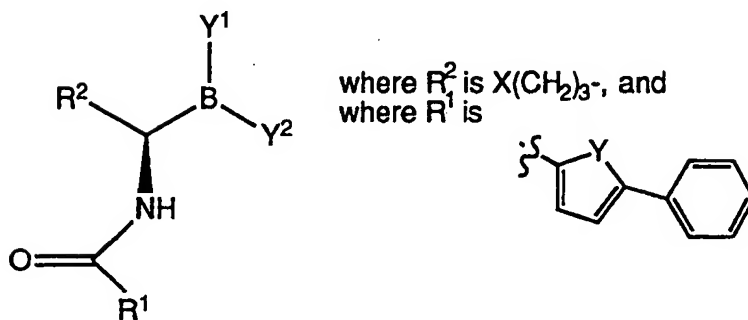
TABLE 7



Ex	X	Y ¹ , Y ²	Phys Data
305	NHC(NH)NH ₂	(+)-pinanediol	
10 306	SC(NH)NH ₂	(+)-pinanediol	II
307	CH ₂ NH ₂	(+)-pinanediol	
308	NHC(NH)NH ₂	H, H	
309	SC(NH)NH ₂	H, H	
310	CH ₂ NH ₂	H, H	

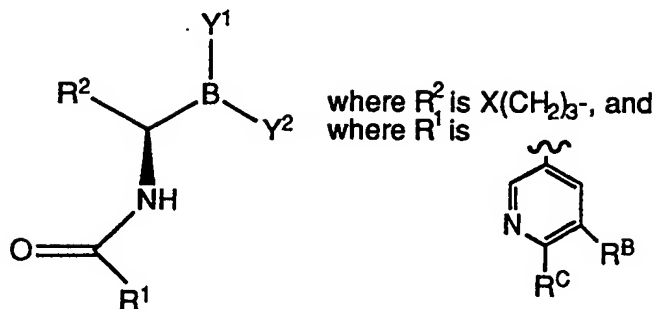
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TABLE 8



	Ex	X	Y	y ¹ , y ²	Phys Data
	311	NHC(NH)NH ₂	O	(+)-pinanediol	
	312	SC(NH)NH ₂	O	(+)-pinanediol	JJ
	313	CH ₂ NH ₂	O	(+)-pinanediol	
5	314	NHC(NH)NH ₂	S	(+)-pinanediol	
	315	SC(NH)NH ₂	S	(+)-pinanediol	
	316	CH ₂ NH ₂	S	(+)-pinanediol	
	317	NHC(NH)NH ₂	O	H, H	
	318	SC(NH)NH ₂	O	H, H	
10	319	CH ₂ NH ₂	O	H, H	
	320	NHC(NH)NH ₂	S	H, H	
	321	SC(NH)NH ₂	S	H, H	
	322	CH ₂ NH ₂	S	H, H	

TABLE 9

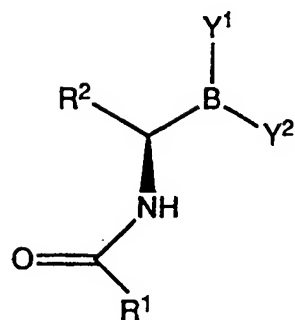


15

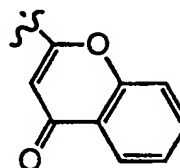
	Ex	X	R ^B	R ^C	y ¹ , y ²	Phys Data
	323	NHC(NH)NH ₂	H	Ph	(+)-pinanediol	
	324	NHC(NH)NH ₂	OBn	H	(+)-pinanediol	
20	325	SC(NH)NH ₂	Ph	H	(+)-pinanediol	KK
	326	SC(NH)NH ₂	H	OBn	(+)-pinanediol	LL
	327	CH ₂ NH ₂	H	Ph	(+)-pinanediol	
	328	CH ₂ NH ₂	OBn	H	(+)-pinanediol	
	329	NHC(NH)NH ₂	H	Ph	H, H	
25	330	NHC(NH)NH ₂	OBn	H	H, H	
	331	SC(NH)NH ₂	H	Ph	H, H	
	Ex	X	R ^B	R ^C	y ¹ , y ²	Phys Data
	332	SC(NH)NH ₂	OBn	H	H, H	

333	CH ₂ NH ₂	H	Ph	H, H
334	CH ₂ NH ₂	OBn	H	H, H

TABLE 10



where R² is X(CH₂)₃-, and
where R¹ is

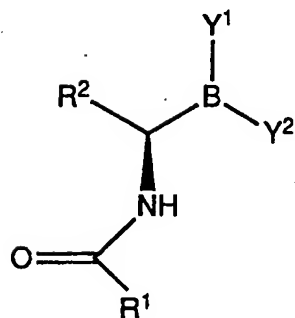


5

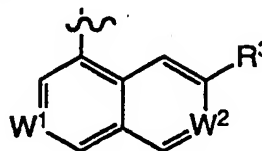
Ex	X	y ¹ , y ²	Phys Data
335	NHC(NH)NH ₂	(+)-pinanediol	
336	SC(NH)NH ₂	(+)-pinanediol	MM
10 337	CH ₂ NH ₂	(+)-pinanediol	
338	NHC(NH)NH ₂	H, H	
339	SC(NH)NH ₂	H, H	
340	CH ₂ NH ₂	H, H	

15

TABLE 11



where R² is X(CH₂)₃-, and
where R¹ is

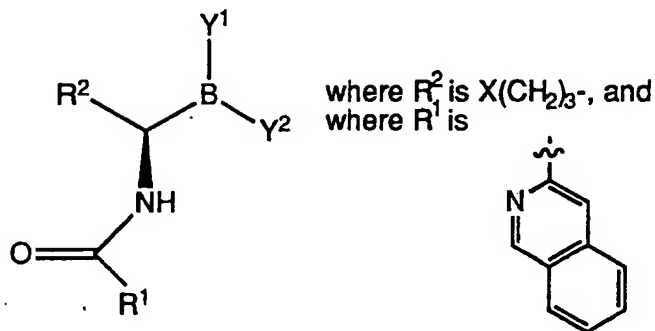


Ex	X	W ¹	W ²	R ³	y ¹ , y ²	Phys
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Data

	341	NHC(NH)NH ₂	N	CH	H	(+)-pinanediol	
	342	SC(NH)NH ₂	N	CH	H	(+)-pinanediol	
	343	CH ₂ NH ₂	N	CH	H	(+)-pinanediol	
5	344	NHC(NH)NH ₂	CH	N	Ph	(+)-pinanediol	
	345	SC(NH)NH ₂	CH	N	Ph	(+)-pinanediol	00
	346	CH ₂ NH ₂	CH	N	Ph	(+)-pinanediol	
	347	NHC(NH)NH ₂	N	CH	H	H, H	
	348	SC(NH)NH ₂	N	CH	H	H, H	
10	349	CH ₂ NH ₂	N	CH	H	H, H	
	350	NHC(NH)NH ₂	CH	N	Ph	H, H	
	351	SC(NH)NH ₂	CH	N	Ph	H, H	
	352	CH ₂ NH ₂	CH	N	Ph	H, H	

TABLE 12

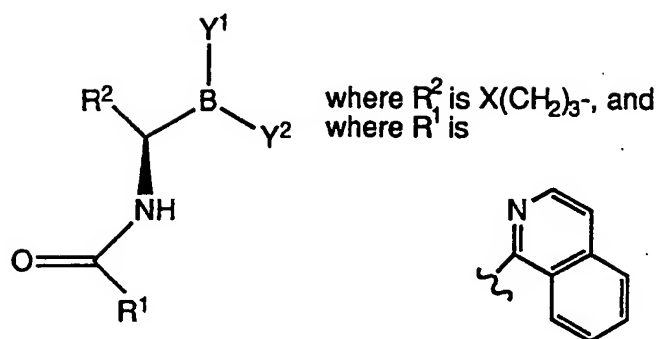


15

Ex	X	Y ¹ , Y ²	Phys Data
353	NHC(NH)NH ₂	(+)-pinanediol	
354	SC(NH)NH ₂	(+)-pinanediol	PP
20	355	CH ₂ NH ₂	(+)-pinanediol
	356	NHC(NH)NH ₂	H, H
	357	SC(NH)NH ₂	H, H
	358	CH ₂ NH ₂	H, H

25

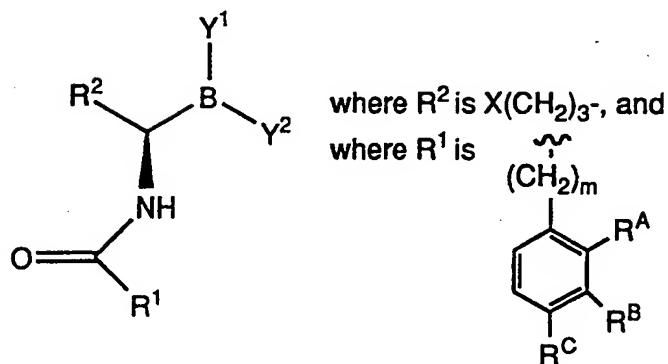
TABLE 13



Ex	X	R^3	Y^1, Y^2	Phys Data
359	SC(NH)NH ₂	H	(+)-pinanediol	NN

5

TABLE 14



10	Ex	X	m	R ^A	R ^B	R ^C	y ¹ , y ²	Phys Data
	SC (NH) NH ₂	2		H	NHCO (CH ₂) ₂ Ph	H	(+)-pinanediol	RR
	SC (NH) NH ₂	2		H	Ph	H	(+)-pinanediol	
	SC (NH) NH ₂	2		H	OPh	Ph	(+)-pinanediol	
	SC (NH) NH ₂	1		H	H	4-pyridyl	(+)-pinanediol	
15	NHC (NH) NH ₂	1		COPh	H	H	(+)-pinanediol	
	NHC (NH) NH ₂	3		H	COPh	H	(+)-pinanediol	
	NHC (NH) NH ₂	3		H	H	COPh	(+)-pinanediol	

Physical Data for Tables 1-14

A: MS (M+H)⁺ = 489; ¹H NMR (400 MHz, CDCl₃, 60 °C)
9.48 (1H, bs), 8.10 (2 H, d, J = 8.1), 8.07 (1 H,
5 bs), 7.75 (1 H, bs), 7.54 (2 H, d, J = 8.3), 7.48 (2
H, d, J = 7.0), 7.35 (3 H, m), 7.06 (4 H, bs), 4.19
(1 H, bd, J = 8.3), 3.1 (2 H, m), 2.84 (1 H, m), 2.29
(1 H, m), 2.12 (1 H, m), 1.96 (1 H, m), 1.75 (6 H,
m), 1.47 (1 H, d, J = 10.2), 1.40 (3 H, s), 1.24 (3
10 H, s), 0.83 (3 H, s).

B: MS (DCI - NH₃), 505 (M + H)⁺.

C: MS (M+H)⁺ = 490.

15

D: MS (M+H)⁺ = 506; ¹H NMR (300 MHz, CDCl₃) 8.15 (2 H,
d, J = 8.4), 7.61 (2 H, d, J = 8.4), 7.52 (2 H, m),
7.38 (3 H, m), 6.47 (1 H, bs), 4.23 (1 H, dd, J =
6.6, 1.9), 3.24 (1 H, m), 3.14, (1 H, m), 2.96, (1 H,
20 m), 2.32 (1 H, m), 2.15 (1 H, m), 1.99 (1 H, m), 1.78
(6 H, m), 1.48 (1 H, d, J = 10.1), 1.42 (3 H, s),
1.27 (3 H, s), 0.86 (3 H, s).

E: mp 145-150 °C.

25

F: MS (DCI - NH₃), 522 (M + H)⁺.

G: HRMS (DCI - NH₃), Calc: 534.2597, Found: 534.2609.

30 H: HRMS (DCI - NH₃), Calc: 534.2597, Found: 534.2605.

I: HRMS (DCI - NH₃), Calc: 534.2597, Found: 534.2609.

J: [α]_D = -14.85° (c = 0.606, MeOH); ¹H NMR (300 MHz,
35 DMSO - d₆) 10.07 (br s, 1 H), 10.05 (br s, 1 H), 8.96
(4 H, br s), 8.08 (1 H, s), 7.71 (1 H, dd, J = 8.1,

1.1), 7.61 (1 H, d, $J = 7.7$), 7.30 - 7.50 (6 H, m),
5.18 (2 H, s), 4.08 (1 H, br d), 3.08 - 3.25 (2 H,
m), 2.50 - 2.65 (1 H, m), 2.15 - 2.30 (1 H, m), 1.97
- 2.10 (1 H, m), 1.40 - 1.90 (8 H, m), 1.31 (3 H, s),
5 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700
(br), 1734, 1646, 1578, 1550, 1440, 1222, 1058 cm^{-1} ;
MS (CI - NH_3), m/e (%) 537.2 (10.2, $M + H - \text{H}_2\text{NCN}^+$),
429.0 (42.8), 277.0 (100); Anal. Calcd for
 $\text{C}_{30}\text{H}_{40}\text{BBBrN}_4\text{O}_5\text{S}$: C, 54.64; H, 6.11; N, 8.50; B, 1.64.
10 Found: C, 54.52; H, 6.16; N, 8.45; B, 1.60.

K: $[\alpha]_D = -15.07^\circ$ ($c = 0.604$, MeOH); ^1H NMR (300 MHz,
DMSO - d_6) 9.98 (1 H, br s), 8.96 (4 H, br s), 7.93 (1
H, narrow m), 7.80 (1 H, app d), 7.64 (1 H, m), 7.56
15 (1 H, app t), 7.25 - 7.42 (5 H, m), 5.13 (2 H, s),
4.11 (1 H, dd, $J = 8.3, 1.7$), 3.30 (3 H, s), 3.10 -
3.25 (2 H, m), 2.57 - 2.68 (1 H, m), 2.15 - 2.30 (1
H, m), 1.97 - 2.10 (1 H, m), 1.48 - 1.90 (7 H, m),
1.44 (1 H, d, $J = 9.9$), 1.31 (3 H, s), 1.24 (3 H, s),
20 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1710,
1647, 1159 cm^{-1} ; MS (CI - NH_3), m/e (%) 593.2 (1.2,
($M + H$) $^+$), 568.3 (22, ($M + \text{NH}_4 - \text{H}_2\text{NCN}^+$), 551.3 (100,
($M + H - \text{H}_2\text{NCN}^+$); Anal. Calcd for $\text{C}_{31}\text{H}_{42}\text{BBBrN}_4\text{O}_5\text{S}$: C,
55.29; H, 6.29; N, 8.32; B, 1.61. Found: C, 55.15;
25 H, 6.21; N, 8.22; B, 1.47.

L: $[\alpha]_D = -14.12^\circ$ ($c = 0.602$, MeOH); ^1H NMR (300 MHz,
DMSO - d_6) 10.09 (1 H, br s), 8.98 (4 H, br s), 7.90
(2 H, d, $J = 8.3$), 7.42 (2 H, d, $J = 8.3$), 4.06 (1 H,
30 d, $J = 7.0$), 3.15 - 3.20 (2 H, m), 2.70 (2 H, q, $J =$
7.7), 2.54 (1 H, m), 2.18 - 2.28 (1 H, m), 1.98 -
2.08 (1 H, m), 1.44 - 1.84 (8 H, m), 1.30 (3 H, s),
1.24 (3 H, s), 1.20 (3 H, t, $J = 7.7$), 0.84 (3 H, s);
IR (KBr) 2600 - 3700 (br), 1646, 1614, 1598, 1570,
35 1500, 1123 cm^{-1} ; MS (DCI - NH_3), m/e (%) 458 (100, (M

+ H)⁺); Anal. Calcd for C₂₄H₃₇BBrN₃O₃S: C, 53.54; H, 6.93; N, 7.81; B, 2.01. Found: C, 53.75; H, 6.98; N, 7.74; B, 1.97.

5 M: [α]_D = -14.21° (c = 0.556, MeOH); ¹H NMR (300 MHz, DMSO - d₆) 10.06 (1 H, br s), 8.95 (4 H, br s), 7.88 (2 H, d, J = 8.1), 7.40 (2 H, d, J = 8.1), 4.06 (1 H, dd, J = 1.7, 8.3), 3.14 - 3.17 (2 H, m), 2.65 (2 H, t, J = 7.5), 2.50 - 2.60 (1 H, m), 2.18 - 2.28 (1 H, m), 1.98 - 2.08 (1 H, m), 1.45 - 1.84 (10 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 0.89 (3 H, t, J = 7.3), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1614, 1598, 1570, 1500, 1446, 1236, 1124, 1082 cm⁻¹; MS (CI - NH₃), m/e (%) 472.2 (13.5, (M + H)⁺), 430.2 (100, (M + H - H₂NCN)⁺), 278.0 (61.9); Anal. Calcd for C₂₅H₃₉BBrN₃O₃S: C, 54.36; H, 7.12; N, 7.61; B, 1.96. Found: C, 54.50; H, 7.18; N, 7.83; B, 1.73.

N: [α]_D = -13.79° (c = 0.602, MeOH); ¹H NMR (300 MHz, DMSO - d₆) 10.03 (1 H, br s), 8.94 (4 H, br s), 7.89 (2 H, d, J = 8.3), 7.45 (2 H, d, J = 8.3), 4.06 (1 H, br d), 3.10 - 3.23 (2 H, m), 2.90 - 3.05 (1 H, m), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.42 - 1.89 (8 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 1.23 (6 H, d, J = 7.0), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1613, 1598, 1123 cm⁻¹; MS (DCI - NH₃), m/e (%) 472 (100, (M + H)⁺), 430 (37, (M + H - H₂NCN)⁺); Anal. Calcd for C₂₅H₃₉BBrN₃O₃S: C, 54.36; H, 7.12; N, 7.61; B, 1.96. Found: C, 54.64; H, 7.17; N, 7.50; B, 1.74.

O: [α]_D = -13.19° (c = 0.364, MeOH); ¹H NMR (300 MHz, DMSO - d₆) 10.03 (1 H, br s), 8.93 (4 H, br s), 7.88 (2 H, d, J = 8.5), 7.40 (2 H, d, J = 8.5), 4.06 (1 H, br d, J = 6.6), 3.15 - 3.20 (2 H, m), 2.67 (2 H, t, J

= 7.7), 2.50 - 2.60 (1 H, m), 2.18 - 2.28 (1 H, m), 1.95 - 2.08 (1 H, m), 1.24 - 1.84 (10 H, m), 1.23 - 1.35 (2 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 0.90 (3 H, t, $J = 7.3$), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1614, 1598, 1500, 1123 cm^{-1} ; MS (CI - NH_3), m/e (%) 486.2 (3.3, $(M + H)^+$), 444.2 (87.1, $(M + H - \text{H}_2\text{NCN})^+$), 292.0 (100); Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{BBBrN}_3\text{O}_3\text{S}$: C, 55.13; H, 7.30; N, 7.42; B, 1.91. Found: C, 54.99; H, 7.22; N, 7.29; B, 2.07.

10

P: $[\alpha]_D = -12.71^\circ$ ($c = 0.598$, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 10.05 (1 H, br s), 8.95 (4 H, br s), 7.90 (2 H, d, $J = 8.6$), 7.59 (2 H, d, $J = 8.6$), 4.06 (1 H, br d), 3.10 - 3.23 (2 H, m), 2.50 - 2.62 (1 H, m), 2.16 - 2.30 (1 H, m), 1.96 - 2.08 (1 H, m), 1.42 - 1.90 (8 H, m), 1.31 (9 H, s), 1.30 (3 H, s), 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1613, 1597, 1498, 1123 cm^{-1} ; MS (DCI - NH_3), m/e (%) 486 (100, $(M + H)^+$), 444 (16, $(M + H - \text{H}_2\text{NCN})^+$); Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{BBBrN}_3\text{O}_3\text{S}$: C, 55.13; H, 7.30; N, 7.42; B, 1.91. Found: C, 55.09; H, 7.45; N, 7.40; B, 1.67.

Q: ^1H NMR (300 MHz, DMSO - d_6) 10.06 (1 H, br s), 8.95 (4 H, br s), 7.88 (2 H, d, $J = 8.5$), 7.40 (2 H, d, $J = 8.5$), 4.06 (1 H, br d, $J = 6.6$), 3.10 - 3.23 (2 H, m), 2.66 (2 H, t, $J = 7.7$), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.40 - 1.90 (10 H, m), 1.20 - 1.38 (12 H, m), 0.80 - 0.90 (6 H, m); IR (KBr) 2500 - 3700 (br), 1646, 1614, 1598, 1500, 1124 cm^{-1} ; MS (DCI - NH_3), m/e (%) 514 (100, $(M + H)^+$), 472 (16, $(M + H - \text{H}_2\text{NCN})^+$); Anal. Calcd for $\text{C}_{28}\text{H}_{45}\text{BBBrN}_3\text{O}_3\text{S}$: C, 56.57; H, 7.63; N, 7.07; B, 1.82. Found: C, 56.19; H, 7.53; N, 6.97; B, 1.99.

35

R: $[\alpha]_D = -11.70^\circ$ ($c = 0.530$, MeOH); ^1H NMR (300 MHz, DMSO - d_6) δ 10.05 (1 H, br s), 8.83 - 9.13 (4 H, br d), 7.88 (2 H, d, $J = 8.3$), 7.43 (2 H, d, $J = 8.3$), 4.06 (1 H, br d), 3.05 - 3.25 (2 H, m), 2.45 - 2.67 (2 H, m), 2.13 - 2.30 (1 H, m), 1.94 - 2.10 (1 H, m), 1.30 - 1.90 (18 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1613, 1598, 1500, 1448, 1122 cm^{-1} ; MS (DCI - NH_3), m/e (%) 512 (100, $(M + H)^+$), 470 (40, $(M + H - \text{H}_2\text{NCN})^+$); Anal. Calcd for $\text{C}_{28}\text{H}_{43}\text{BBBrN}_3\text{O}_3\text{S}$: C, 56.77; H, 7.32; N, 7.09; B, 1.82. Found: C, 56.49; H, 7.38; N, 6.96; B, 1.75.
S: HRMS (DCI - NH_3), Calc: 577.3019, Found: 577.3025.

15 T: $[\alpha]_D = -8.31^\circ$ ($c = 0.614$, MeOH); ^1H NMR (300 MHz, DMSO - d_6) δ 9.98 (1 H, br s), 8.95 (4 H, br s), 7.93 (2 H, d, $J = 8.8$), 7.11 (2 H, d, $J = 8.8$), 4.00 - 4.10 (3 H, m), 3.10 - 3.23 (2 H, m), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.37 - 1.90 (12 H, m), 1.29 (3 H, s), 1.24 (3 H, s), 0.94 (3 H, t, $J = 7.4$), 0.84 (3 H, s); IR (KBr) 2500 - 3700 (br), 1646, 1608, 1498, 1262, 1124 cm^{-1} ; MS (DCI - NH_3), m/e (%) 502 (100, $(M + H)^+$), 460 (28, $(M + H - \text{H}_2\text{NCN})^+$); Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{BBBrN}_3\text{O}_4\text{S}$: C, 53.62; H, 7.10; N, 7.21; B, 1.86. Found: C, 53.61; H, 7.09; N, 7.20; B, 1.78.

U: HRMS (DCI - NH_3), Calc: 513.2707, Found: 513.2702.

30 V: HRMS (DCI - NH_3), Calc: 555.3165, Found: 555.3176.

W: HRMS (DCI - NH_3), Calc: 579.2812, Found: 579.2801.

X: HRMS (DCI - NH_3), Calc: 450.2962, Found: 450.2958.

35 Y: HRMS (DCI - NH_3), Calc: 640.3016, Found: 640.3022.

Z: $[\alpha]_D = -8.80^\circ$ ($c = 0.602$, MeOH); ^1H NMR (300 MHz, DMSO - d_6) 10.03 (1 H, br s), 9.25 (1 H, br s), 8.96 (4 H, br s), 7.92 (1 H, d, $J = 1.5$), 7.72 (1 H, dd, $J = 8.1, 1.5$), 7.25 - 7.50 (6 H, m), 5.17 (2 H, s), 4.08 (1 H, dd, $J = 8.1, 1.5$), 3.08 - 3.27 (2 H, m), 2.65 (2 H, br t), 2.50 - 2.60 (1 H, m), 2.15 - 2.30 (1 H, m), 1.95 - 2.08 (1 H, m), 1.40 - 1.90 (10 H, m), 1.30 (3 H, s), 1.24 (3 H, s), 1.15 - 1.38 (2 H, m, buried underneath methyl absorptions), 0.77 - 0.95 (6 H, m); IR (KBr) 2500 - 3700 (br), 1704, 1646, 1572, 1539, 1453, 1234, 1123, 1056 cm^{-1} ; MS (CI - NH_3), m/e (%) 593.2 (1.3, $(\text{M} + \text{H} - \text{H}_2\text{NCN})^+$), 485.2 (42.7), 333.0 (100); Anal. Calcd for $\text{C}_{34}\text{H}_{48}\text{BBBrN}_4\text{O}_5\text{S}$: C, 57.07; H, 6.76; N, 7.83; B, 1.51. Found: C, 57.17; H, 6.84; N, 7.76; B, 1.41.

AA: ^1H NMR (300 MHz, DMSO - d_6) 9.98 (1 H, br s), 8.98 (4 H, br s), 7.77 - 7.92 (2 H, m), 7.08 - 7.55 (6 H, m), 4.90 - 5.30 (2 H, m), 4.09 (1 H, br d), 3.04 - 3.35 (5 H, m), 2.35 - 2.65 (3 H, m), 2.15 - 2.30 (1 H, m), 1.97 - 2.10 (1 H, m), 1.37 - 1.93 (10 H, m), 1.31 (3 H, s), 1.24 (3 H, s), 1.10 - 1.37 (2 H, m, buried underneath methyl absorptions), 0.72 - 0.93 (6 H, m); MS (CI - NH_3), m/e (%) 649.4 (1.9, $(\text{M} + \text{H})^+$), 624.4 (31, $(\text{M} + \text{NH}_4 - \text{H}_2\text{NCN})^+$), 607.2 (100, $(\text{M} + \text{H} - \text{H}_2\text{NCN})^+$), 455.0 (39), 444.0 (29.8); Anal. Calcd for $\text{C}_{35}\text{H}_{50}\text{BBBrN}_4\text{O}_5\text{S}$: C, 57.62; H, 6.91; N, 7.68; B, 1.48. Found:

C, 57.37; H, 6.86; N, 7.64; B, 1.40.

BB: HRMS (DCI - NH_3), Calc: 520.2805, Found: 520.2796.

CC: HRMS (DCI - NH_3), Calc: 560.2390, Found: 560.2407.

DD: HRMS (DCI - NH_3), Calc: 596.2060, Found: 596.2055.

EE: HRMS (DCI - NH₃), Calc: 546.2597, Found: 546.2604.
FF: HRMS (DCI - NH₃), Calc: 534.2597, Found: 534.2609.
5 GG: HRMS (DCI - NH₃), Calc: 532.2441, Found: 532.2445.
HH: HRMS (DCI - NH₃), Calc: 532.2441, Found: 532.2452.
II: HRMS (DCI - NH₃), Calc: 480.2493, Found: 480.2492.
10 JJ: HRMS (DCI - NH₃), Calc: 496.2441, Found: 496.2449.
KK: HRMS (DCI - NH₃), Calc: 507.2601, Found: 507.2592.
15 LL: HRMS (DCI - NH₃), Calc: 537.2667, Found: 537.2685.
MM: HRMS (DCI - NH₃), Calc: 498.2233, Found: 498.2231.
NN: HRMS (DCI - NH₃), Calc: 481.2445, Found: 481.2442.
20 OO: HRMS (DCI - NH₃), Calc: 557.2758, Found: 557.2754.
PP: HRMS (DCI - NH₃), Calc: 5481.2445, Found: 481.2440.
25 QQ: HRMS (NH₃) - CI/DEP), Calc: 503.3193, Found: 503.3199.
RR: HRMS (DCI-NH₃), Calc: 605.333; Found: 605.3325.

30

Utility

The compounds of formula (I) are useful as inhibitors of trypsin-like enzymes, notably human thrombin, plasma kallikrein and plasmin. Because of their inhibitory action, these compounds are indicated for
35 use in the prevention or treatment of physiological

reactions catalyzed by the aforesaid enzymes such as blood coagulation and inflammation.

As an illustration of the above, the biological activity of compounds of the present invention is demonstrated by their *in vitro* inhibition of synthetic substrate hydrolysis by human thrombin S-2238 Chromogenic Assay (IC₅₀). The synthetic substrate H-D-Phe-Pip-Arg-pNA (S-2238, Kabi) is cleaved by thrombin, liberating the *p*-nitroanalide group which absorbs light at 405 nm. Enzyme activity is measured in both the presence and absence of inhibitor. A decrease in absorbance at 405 nm in the presence of inhibitor is indicative of thrombin inhibition.

A mixture of 10 μ L human thrombin (Enzyme Research Laboratories, Inc.) at an activity of approximately 7 units/mL, 10 μ L of the inhibitor (normally at a concentration of 10^{-3} M or less), and 160 μ L buffer (0.15 M NaCl, 10 mM HEPES, 10 mM Tris, 1 g/L PEG 8,000, pH 7.4) are incubated for 10 minutes at room temperature. To this mixture is added 20 μ L of the synthetic substrate S-2238 at a concentration of 1 mM and the reaction allowed to occur for 10 minutes, after which absorbance at 405 nm is determined.

Using the methodology described above, representative compounds of this invention were evaluated and found to exhibit an IC₅₀ of less than 1 mM, thereby confirming the utility of the compounds of the invention as effective thrombin inhibitors.

Since the compounds of formula (I) have anti-thrombogenic properties, they may be employed when an anti-thrombogenic agent is indicated, such as for control of the coagulation or the fibrinolysis system in mammals or they may be added to blood for the purpose of preventing coagulation or the blood due to

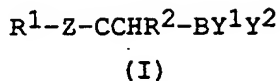
contact with blood collecting or distribution containers, tubing or apparatus.

Generally, these compounds may be administered orally or parenterally to a host to obtain an anti-thrombogenic effect. The dosage of the active compound depends on the mammalian species, body weight, age, and mode of administration as will be obvious to one skilled in the art. In the case of large mammals such as humans, the compounds may be administered alone or in combination with pharmaceutical carriers or diluents at a dose of from 0.02 to 15 mg/Kg to obtain the anti-thrombogenic effect, and may be given as a single dose or in divided doses or as a sustained release formulation.

Pharmaceutical carriers or diluents are well known and include sugars, starches and water, which may be used to make tablets, capsules, injectable solutions or the like which can serve as suitable dosage forms for administration of the compounds of this invention. Remington's Pharmaceutical Sciences, A. Osol, is a standard reference text which discloses suitable pharmaceutical carriers and dosage forms. The disclosure of this text is hereby incorporated by reference for a more complete teaching of suitable dosage forms for administration of the compounds of this invention.

WHAT IS CLAIMED IS:

1. A compound of formula (I)



5

wherein

Y^1 and Y^2 are independently

- 10
- a) -OH
 - b) -F,
 - c) - NR^3R^4 , or
 - d) C1-C8- alkoxy;

Y^1 and Y^2 when taken together can form

- 15
- a) a cyclic boron ester where said chain or ring contains from 2 to 20 carbon atoms and, optionally, a heteroatom which can be N, S, or O,
 - b) a divalent cyclic boro amide where said chain or ring contains from 2 to 20 carbon atoms,
 - 20 c) a cyclic boro amide-ester where said chain or ring contains from 2 to 20 carbon atoms;

Z is

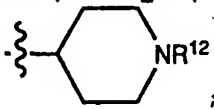
- 25
- a) - $(\text{CH}_2)_m\text{CONR}^8\text{-}$,
 - b) - $(\text{CH}_2)_m\text{CSNR}^8\text{-}$,
 - c) - $(\text{CH}_2)_m\text{SO}_2\text{NR}^8\text{-}$,
 - d) - $(\text{CH}_2)_m\text{CO}_2\text{-}$,
 - e) - $(\text{CH}_2)_m\text{C(S)O-}$, or
 - f) - $(\text{CH}_2)_m\text{SO}_2\text{O-}$;

30

R^1 is

- 35
- a) - $(\text{CH}_2)_p\text{-aryl}$, wherein aryl is phenyl, naphthyl or biphenyl substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl,

C2--C10-alkynyl, $-R^8$, $-OR^8$, methylenedioxy,
 $-NO_2$, $-CF_3$, $-S(O)_rR^7$, NR^8R^9 , $-COR^8$, $-CO_2R^8$,

$-CONR^8R^9$, NR^8COR^9 , $NR^8CO_2R^9$,  ;

5 b) heteroaryl, wherein heteroaryl is an
 unsubstituted or monosubstituted or
 disubstituted

10 i) 5- or 6-membered aromatic ring, which
 contains from 1 to 3 heteroatoms selected
 from the group consisting of O, N, and S,

ii) quinolinyl,

iii) isoquinolinyl,

iv) benzopyranyl,

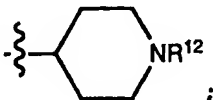
v) benzothiophenyl,

15 vi) benzofuranyl,

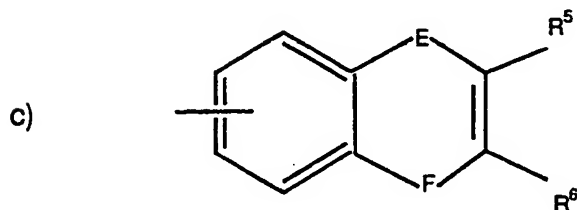
vii) 5,6,7,8-tetrahydroquinolinyl.

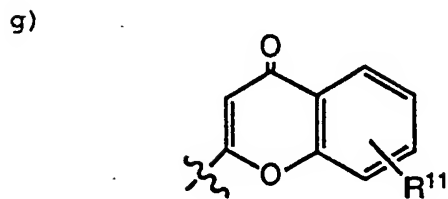
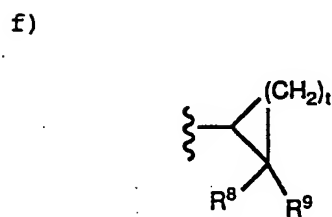
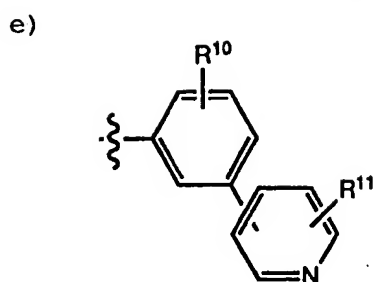
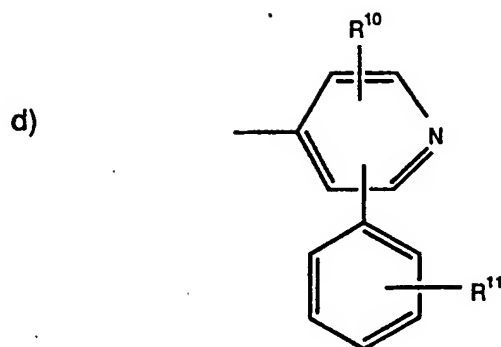
viii) 5,6,7,8-tetrahydroisoquinolinyl

20 and wherein the substituents are members selected
 from the group consisting of halo (F, Cl, Br, I,
 $-CN$, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-
 alkenyl, C2-C10-alkynyl, $-R^8$, OR^8 , NO_2 , $-CF_3$,
 $-S(O)_rR^7$, NR^8R^9 , $-COR^8$, $-CONR^8R^9$, NR^8COR^9 ,
 $NR^8CO_2R^9$,



25





R² is

- a) $-(CH_2)_n-NHC(NH)NH_2$,
 b) $-(CH_2)_n-NHC(NH)NHCOCH_3$,
 c) $-(CH_2)_n-SC(NH)NH_2$,
 e) $-(CH_2)_n-SC(NH)_2$, or
 f) $-(CH)_n-NH(2\text{-pyridyl})$;

R³ is H, phenyl or C1-C4-alkyl;

R⁴ is H, or phenylsulfonyl;

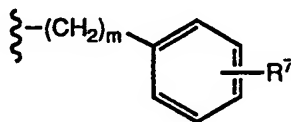
R⁵ and R⁶ are hydrogen or when taken together form a six membered aromatic ring optionally substituted with one, two or three substituents selected from the group consisting of halo (F, Cl, Br, I), -CN, C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, -OR⁸, -NO₂, -CF₃, -S(O)_rR⁷, -NR⁸R⁹, -COR⁸, -COR₂R⁸, -CONR⁸R⁹, phenyl, benzyl, phenylethyl;

R⁷ is

- a) phenyl,
- b) C1-C4-alkyl,
- c) C1-C4-alkoxy, or
- d) -CF₃;

R⁸ and R⁹ are independently

- a) H,
- b)



- c) C3-C7-Cycloalkyl,
- d) C1-C8-alkyl;

R¹⁰ and R¹¹ are independently

- a) halo (F, Cl, Br, I),
- b) -CN,
- c) C1-C10-alkyl,
- d) C3-C8-cycloalkyl,
- e) C2-C10-alkenyl,
- f) C2-C10-alkynyl,
- g) -OR⁸,
- h) NO₂,
- i) -CF₃,
- j) -S(O)_rR⁷,
- k) -NR⁸R⁹,
- l) -COR⁹,
- m) -CO₂R⁸, or
- n) -CONR⁸R⁹;

R¹² is

- a) H,
- b) C1-C4-alkyl,
- 5 c) phenyl
- d) benzyl,
- e) -COR⁷
- f) -SO₂R⁷

m is 0 to 6;

10 n is 3 or 4;

p is 0 to 2;

r is 0 to 2;

t is 1 to 5

E is -CO-, -SO₂-, -CH₂- or a single bond,

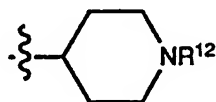
15 F is -CO-, and

pharmaceutically acceptable salts thereof.

2. A compound of Claim 1 wherein:

R¹ is phenyl containing 1-3

20 substituents selected from the series halo (F, Cl, Br, I), C1-C10-alkyl, C3-C8-cycloalkyl, C2-C10-alkenyl, C2-C10-alkynyl, -R⁸, -OR⁸, -NO₂, -CF₃, -S(O)_rR⁷, -NR⁸R⁹, -COR⁸, -CO₂R⁸, CONR⁸R⁹, NR⁸COR⁹, and



25 ; and

R₂ is

- a) -(CH₂)₃-NHC(NH)NH₂, or
- b) -(CH₂)₃-SC(NH)NH₂.

30 3. A compound of Claim 2 wherein Z is -(CH₂)_mCONR⁸-.

4. A compound of Claim 3 selected from the group consisting of

N¹-(4-phenylbenzoyl)-(R)-boroarganine, hydrochloride,

- N¹-(3-phenoxybenzoyl)-(R)-boroarginine, hydrochloride,
N¹-(1-fluorenonyl)-(R)-boroarginine, hydrochloride,
N¹-(4-[butyl]benzoyl)-(R)-boroarginine, hydrochloride,
N¹-(2-benzoylbenzoyl)-R-boroarginine, hydrochloride,
5 N¹-(5-phenyl-2-furol)-R-boroarginine, hydrochloride,
N¹-(3-[N-benzyloxycarbonyl-N-methylamino]-4-[1-butyl]-
benzoyl)-(R)-boroarginine, hydrochloride,
N¹-(2-phenyl-4-isoquinolyl)-(R)-boroarginine,
hydrochloride,
10 N¹-(4-cyclohexylbenzoyl)-(R)-boroarginine, hydrochloride
N¹-(2-methyl-4-phenylbenzoyl)-(R)-boroarginine,
hydrochloride, or
5. A pharmaceutical composition comprising a
15 pharmaceutically suitable carrier and a
therapeutically effective amount of a compound of any
one of claims 1 through 4.
6. A method of treating a physiological disorder in a
20 warm blooded animal catalyzed by trypsin-like enzymes
comprising administering to an animal in need of such
treatment an effective amount of a compound of any
one of claims 1 through 4.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 94/02965

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07F5/02 A61K31/69

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 471 651 (SANDOZ LTD/SANDOZ-PATENT-G MBH/SANDOZ-ERFINDUNGEN) 19 February 1992 cited in the application see the whole document ---	1-6
A	WO,A,92 07869 (KAKKAR, V.V. ET AL.) 14 May 1992 see the whole document ---	1-6
A	EP,A,0 293 881 (E.I. DU PONT DE NEMOURS AND COMPANY) 7 December 1988 cited in the application see the whole document -----	1-6

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

7 June 1994

Date of mailing of the international search report

14. 06. 94

Name and mailing address of the ISA

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Authorized officer

Rinkel, L

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 94/ 02965

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 6 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 94/02965

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0471651	19-02-92	AU-B- 643312	11-11-93
		AU-A- 8179291	20-02-92
		CA-A- 2048953	14-02-92
		JP-A- 4330094	18-11-92
		US-A- 5288707	22-02-94

WO-A-9207869	14-05-92	AU-B- 636521	29-04-93
		AU-A- 8900791	26-05-92
		EP-A- 0509080	21-10-92
		JP-T- 5504775	22-07-93

EP-A-0293881	07-12-88	US-A- 5187157	16-02-93
		AU-B- 623592	21-05-92
		AU-A- 1733288	08-12-88
		CA-A- 1328332	05-04-94
		DE-A- 3878991	15-04-93
		JP-A- 1063583	09-03-89
		US-A- 5242904	07-09-93
		US-A- 5250720	05-10-93
